ORIGINAL RESEARCH

Quantifying the Association Between Physical Activity and Cardiovascular Disease and Diabetes: A Systematic Review and Meta-Analysis

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***Background*—**The relationships between physical activity (PA) and both cardiovascular disease (CVD) and type 2 diabetes mellitus (T2DM) have predominantly been estimated using categorical measures of PA, masking the shape of the dose-response relationship. In this systematic review and meta-analysis, for the very first time we are able to derive a single continuous PA metric to compare the association between PA and CVD/T2DM, both before and after adjustment for a measure of body weight.

***Methods and Results*—**The search was applied to MEDLINE and EMBASE electronic databases for all studies published from January 1981 to March 2014. A total of 36 studies (3 439 874 participants and 179 393 events, during an average follow-up period of 12.3 years) were included in the analysis (33 pertaining to CVD and 3 to T2DM). An increase from being inactive to achieving recommended PA levels (150 minutes of moderate-intensity aerobic activity per week) was associated with lower risk of CVD mortality by 23%, CVD incidence by 17%, and T2DM incidence by 26% (relative risk [RR], 0.77 [0.71–0.84]), (RR, 0.83 [0.77–0.89]), and (RR, 0.74 [0.72–0.77]), respectively, after adjustment for body weight.

***Conclusions*—**By using a single continuous metric for PA levels, we were able to make a comparison of the effect of PA on CVD incidence and mortality including myocardial infarct (MI), stroke, and heart failure, as well as T2DM. Effect sizes were generally similar for CVD and T2DM, and suggested that the greatest gain in health is associated with moving from inactivity to small amounts of PA. **(*J Am Heart Assoc*. 2016;5:e002495 doi: 10.1161/JAHA.115.002495)**

Key Words: cardiovascular diseases • meta-analysis • physical activity • systematic review

Insufficient physical activity (PA) is a key risk factor for noncommunicable diseases such as cardiovascular diseases (CVD), cancer and diabetes mellitus.[1] CVD is the number 1 cause of death globally, with 17.5 million deaths from CVD and 1.5 million deaths from diabetes in 2012, representing 31% and 2.7% of global deaths, respectively.[2,3]

It has been over half a century since the pioneering studies of bus drivers and then longshoremen, which first established the beneficial impact of PA upon CVD risk.[2,3] More recently, in 2010 the UK Chief Medical Officer Sir Liam Donaldson declared that the benefits of regular PA on health, longevity, and well-being "easily surpass the effectiveness of any drugs or other medical treatment."[4]

Current international recommendations for PA are to achieve at least 150 minutes per week of moderate-intensity aerobic PA, or 75 minutes per week of vigorous PA,[5,6] and a

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Accompanying Tables S1 through S6 and Figures S1 through S20 are available at http://jaha.ahajournals.org/content/5/9/e002495/DC1/embed/inline-supplementary-material-1.pdf

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higher level of 300 minutes per week of moderate-intensity PA has been recommended to reduce the risk of cancer.[7] These recommendations were typically constructed on systematic reviews and meta-analysis of epidemiological studies; however, these reviews were not without limitations. Many only assessed the benefits of a single domain or facet of PA, such as Lee and Paffenbarger,[8] which examines only walking and recreational activity. Most had pooled results based on different ranges of categorical exposure measures (eg, "high" or "low"), for example, Fujita et al.,[9] which compares the sole domain of walking on mortality, or Woodcock et al.,[10] which focuses on "nonvigorous" physical activity. Furthermore, existing reviews, such as Jeon et al.,[11] do not explore the risk reductions after adjusting for body weight and therefore do not allow for an assessment of the independent effect of PA on health outcomes, and at least part of the observed effect is likely to be mediated by maintenance of healthy weight status.

The aim of this study was to conduct a systematic review and meta-analysis to draw together the epidemiological studies that assesses the independent association between PA levels and both CVD and type 2 diabetes mellitus (T2DM) outcomes, using a single continuous metric and adjusting for body weight. In order to make comparable results across disease domains, exposure data for physical activity was converted to a common continuous metric of metabolic equivalent of task (MET) hours per week. Although subject to limitations from original studies, this metric allowed us to study results in order to reflect international PA guidelines. More important, it also allowed us to estimate the relative risk (RR) associated with a unit increase in PA at any activity level, and to explore the dose-response relationship between PA and CVD or T2DM outcomes.

Methods

Eligibility Criteria

Studies considered for inclusion were prospective cohort studies that measured PA levels where at least 2 of the following domains were measured: leisure, household, active travel, and occupational activity.

Estimates of the RR for incidence of or mortality from CVDs or T2DM in participants free of disease at baseline had to be reported. Studies that provided estimates for total CVD were included under the main CVD incidence/mortality results. Otherwise, any studies that reported individual CVD outcomes, such as heart failure or myocardial infarct (MI), were included in separate meta-analyses.

In addition, the RR had to be adjusted for a measure of body weight (eg, continuous measurements of body weight, body mass index, waist circumference, etc., or binary measures of overweight, obesity, etc.). For consistency, all such measures are referred to as "body weight." If multiple studies measuring the same outcome were published from the same cohort, preference was given to that with the most years of follow-up in the analysis. Studies were excluded if the PA measure was one of fitness, as opposed to a measure of time or volume of PA. Only studies published in English were included.

Search Strategy

Relevant studies were identified by searching electronic databases and supplemented by scanning the reference lists of included studies and relevant systematic reviews. The search was applied to MEDLINE and EMBASE electronic databases for all studies published from January 1981 to March 2014. Key terms, among others, included "physical activity," "cardiovascular diseases," "stroke," "heart diseases," and "mortality." The complete search strategy is attached as supplemental online material.

Study Selection and Data Extraction

Identified titles and abstracts were initially obtained through application of the search strategy, and these were divided equally among 3 authors to be screened for inclusion on the basis of title, with a fourth reviewer cross-checking a 10% sample of exclusion decisions. The abstracts of studies included after the initial screening were then independently assessed by 2 reviewers for inclusion in the review, with discrepancies referred to a third reviewer and resolved through discussion. A single reviewer reviewed full-text articles, with a second reviewer cross-checking undecided cases and a random 10% sample of excluded articles. A single reviewer performed data extraction, with a 10% sample check conducted by a second reviewer. If any discrepancies arose between reviewers, these were referred to a third reviewer for discussion.

Assessment of Study Quality

A quality criteria scale at the study level was developed using applicable elements from the Newcastle-Ottawa scale for cohort studies.[12] The developed scale was piloted on 10 studies and refined accordingly, and is displayed in Table S1, along with the assessments of quality for each included study. This scale was previously used in the meta-analysis of walking and cycling by Kelly et al.[13]

Conversion to Standard PA Units

RRs with SEs were obtained from each study for the various reported levels of PA in relation to the reported health

outcomes. The PA exposure in each study was converted to MET hours per day above that expended by the baseline group (referred to throughout as the inactive group) in order to quantify the association on a comparable scale.

One MET is defined as 1 kcal/kg and is approximately equivalent to the energy cost of sitting quietly.[14] This unit was chosen because it provided a continuous variable that could be converted to a single RR estimate for a selected change in volume of PA. Conversion to this scale was performed with reference to the Physical Activity Compendium,[14] which was developed for use in epidemiological studies to standardize the assignment of MET intensities in PA questionnaires.

If PA exposure estimates were not directly reported in the form of MET hours, the Physical Activity Compendium was used to convert the information provided about the amount of PA conducted to our standard unit to reflect the time and intensity of activity. Any reference to "moderate" PA was assigned a value of 4.5 METs and vigorous activity a value of 6.5 METs, based on World Health Organization recommendations.[5] Using the compendium, it was decided to assign any references to "inactive behavior" a value of 1.5 METs, and "light activity" a value of 2.5 METs, and average body weights of 84 and 71 kg[15] were assigned to men and women, respectively, where no other information was provided by the studies.

The rules for converting physical activity measures to a standard metric of "Additional MET h/day" are listed in Table S2.

Statistical Analysis

The relationship between RR and PA was assessed using regression analysis for each study individually. In all cases, it was assumed that the relationship between relative risk and MET hours per week followed a 0.25 power transformation (ie, $RR=1+b\times MET^{0.25}$, where b is a regression coefficient). Additional analyses, namely, both linear and log linear associations, and power transformations of 0.375, 0.50, and 0.75 were also conducted to assess the sensitivity of the findings to the method of parameterising the dose-response relationship. The 0.25 power transformation was chosen for the primary outcome measures because it closely models the observed findings from previous studies that the RR for chronic disease falls quickly with a small addition of PA, but further increases of PA produce rapidly diminishing returns. This transformation has previously been used in a meta-analysis of the effect of PA on all-cause mortality[10] using the Alaike's Information Criterion, in order to select the transformation that best fits the data.[16]

Additionally, a categorical analysis was conducted, where the dose-response relationship was assessed nonparametrically, as previously conducted by Kelly et al.[13] For this analysis, data lines were grouped into three categories (0.1–12.0; 12.1–29.5; 29.6+ MET h/week) and meta-analyses within these 3 PA categories were conducted. The 3 categories refer to tertiles of data points collected from the studies.

For each meta-analysis where the dose-response relationship is described parametrically, the same dose-response relationship was assumed for each individual study, and the dose-response parameter was estimated separately for each study. The meta-analysis was then conducted on the dose-response parameter, with an average value of SE from the PA groups included in each study. Using this method, results could be reported at any value of additional PA, and we have chosen to report results for an increase of 11.25 MET h/week—equivalent to moving from inactive behavior to achieving international PA recommendations. The reported results using the primary outcome measures can also be used to determine the modeled association between PA and the health outcome at any level of PA using a method described in Table 1.

Random-effects meta-analyses were performed, because of the high degree of heterogeneity in the populations under investigation and follow-up time.[17] The heterogeneity between studies in the meta-analyses was assessed using the I^2 statistic. For each health outcome, 2 sets of meta-analyses were conducted using Stata software (version 12; StataCorp LP, College Station, TX): (1) with RRs adjusted for body weight, including all identified studies (primary outcome); (2) with RRs *not* adjusted for body weight, including only studies where RRs were also available without adjustment for body weight. Here, "RRs adjusted for body weight" were taken from the fully adjusted models reported in the included studies, and "RRs *not* adjusted for body weight" were taken from the models adjusting for the most covariates without inclusion of a measure of body weight. Funnel plots were analyzed to assess the possibility of small-study or publication bias. A sensitivity analysis was conducted by restricting results to studies that achieved at least 6 of the 8 quality criteria. Metaregression was performed to explore whether heterogeneity in the results could be explained by study-level variables, including achievement of each of the 8 quality criteria, the sex of participants, mean age of participants, presence of active travel, recreational, occupational, and household domains in the PA measurement, mean follow-up years, and geography.

Review Registration

The protocol was registered with the PROSPERO database: CRD42014009655.

Table 1. Deriving a Modeled Estimate of the Association Between PA and Health Outcomes at Any Level of PA Using the Results From These Meta-Analyses

The results reported in this article (displayed in Table 4) collapse the modeled relationship between PA and health outcomes across a continuous PA metric to a single parameter in order to provide comparable results across disease outcomes. These parameters can be used to estimate the modeled association between PA and health outcome for the difference between any two levels of PA. For example, the meta-analysis of CVD incidence using an *Additional* or *Marginal* METs approach suggests that the RR for a change from 0 MET h/day to 1.61 MET h/day (equivalent to 11.25 MET h/week) is 0.83. These values can be put into equation (1) to obtain the estimate b=−0.15.

$$RR = 1 + b\ \text{MET hr/day}^{0.25} \quad (1)$$

This can then be used to estimate the RR for a unit increase of MET h/day at any PA level. For example, the RR of CVD incidence associated with a change from 2 to 5 MET h/day is estimated as follows:

$$RR_2 = 1 - 0.15 \times 2^{0.25} = 0.82$$

$$RR_5 = 1 - 0.15 \times 5^{0.25} = 0.77$$

$$RR_{2\to5} = \frac{RR_5}{RR_2} = 0.94$$

CVD indicates cardiovascular disease; MET, metabolic equivalent of task; PA, physical activity; RR, relative risk.

Ethical approval/institutional review board approval was not required.

Results

The initial literature searches produced 16 628 titles. After a review of the titles and abstracts, 329 articles were reviewed in full, as detailed in the study flow chart (Figure 1). An additional 8 studies were identified by scanning reference lists of the included studies. The majority of the excluded studies only measured 1 domain of PA or did not adjust for any measure of obesity. Thirty-six studies were included in the final review (listed in Table S3), of which 33 contributed to CVD meta-analyses and 3 contributed to the T2DM meta-analyses.

Table 2 provides a summary of the results of the meta-analyses for estimates both with and without adjustment for body weight and also displays the total number of data points and incidents for each disease outcome. Five data points had to be excluded from meta-analyses because they pertained to conditions for which we only had 1 result, such as Wattanakit et al.,[18] which was the only study to report the PA effect on venous thromboembolism incidence. These studies are listed in Table S4. In addition, 3 studies were removed in the review stage because of overlapping cohorts.

More specifically, Figure 2 graphically outlines RR results for the CVD mortality studies plotted against the amount of PA in our standardized metric.

The 0.25 power transformation is chosen as the preferred transform in this article because demonstrates a better fit to the data; the r^2 value for this transformation was 0.75 compared to 0.29 for the log linear transformation. In terms of the dose-response relationship, the incremental change in risk for 3 differing intensities of PA (low, medium, and high) are listed in Table 3. In general, we noted that the greatest rate of reduction occurs in the first category, that is, as you move from low to medium amounts of PA rather than from medium to high.

Cardiovascular Disease Meta-Analyses

The 33 studies included in the CVD meta-analyses were conducted in Europe (n=13), the United States (n=13), and the rest of the world (n=7). They included a total of 1 683 693 participants, with 89 493 events occurring during an average follow-up period of 12.8 years. The number of data points pooled for each health outcome was as follows: 5 for CVD incidence, 14 for CVD mortality, and 9 for stroke incidence; 6 for CHD incidence, 2 for CHD mortality, 5 for heart failure incidence, and 2 for MI incidence.

Increasing PA by 11.25 MET h/week was associated with a significant decrease in risk for all of the cardiovascular outcomes. The protective association for CVD mortality (RR, 0.77) was greater than for CVD incidence (RR, 0.83), a result that was also shown when restricting both meta-analyses to studies that reported results for both CVD mortality and incidence. Figure 3 displays the meta-analysis of the effect of PA on CVD mortality after adjustment for body weight for the included studies. The meta-analyses for the remaining conditions are shown in Figures S1 through S7.

The results that were adjusted for body weight were only slightly attenuated in comparison with the results that were not adjusted for body weight. The greatest effect of body weight adjustment was noted in the RR of CVD mortality, which reduced from 0.66 (unadjusted) to 0.77 (adjusted for body weight).

The meta-analysis results for the various subcategories of CVD outcomes (such as MI incidence) showed that the estimated RRs were very similar to CVD as a whole. The 0.25 power transformation for overall CVD incidence was 0.83, versus 0.82 for stroke incidence, 0.80 for CHD incidence, 0.81 for heart failure incidence, and 0.75 for MI incidence. The dose-response graphs (Figures S8 and S9) show that the greatest risk reduction was observed when moving from

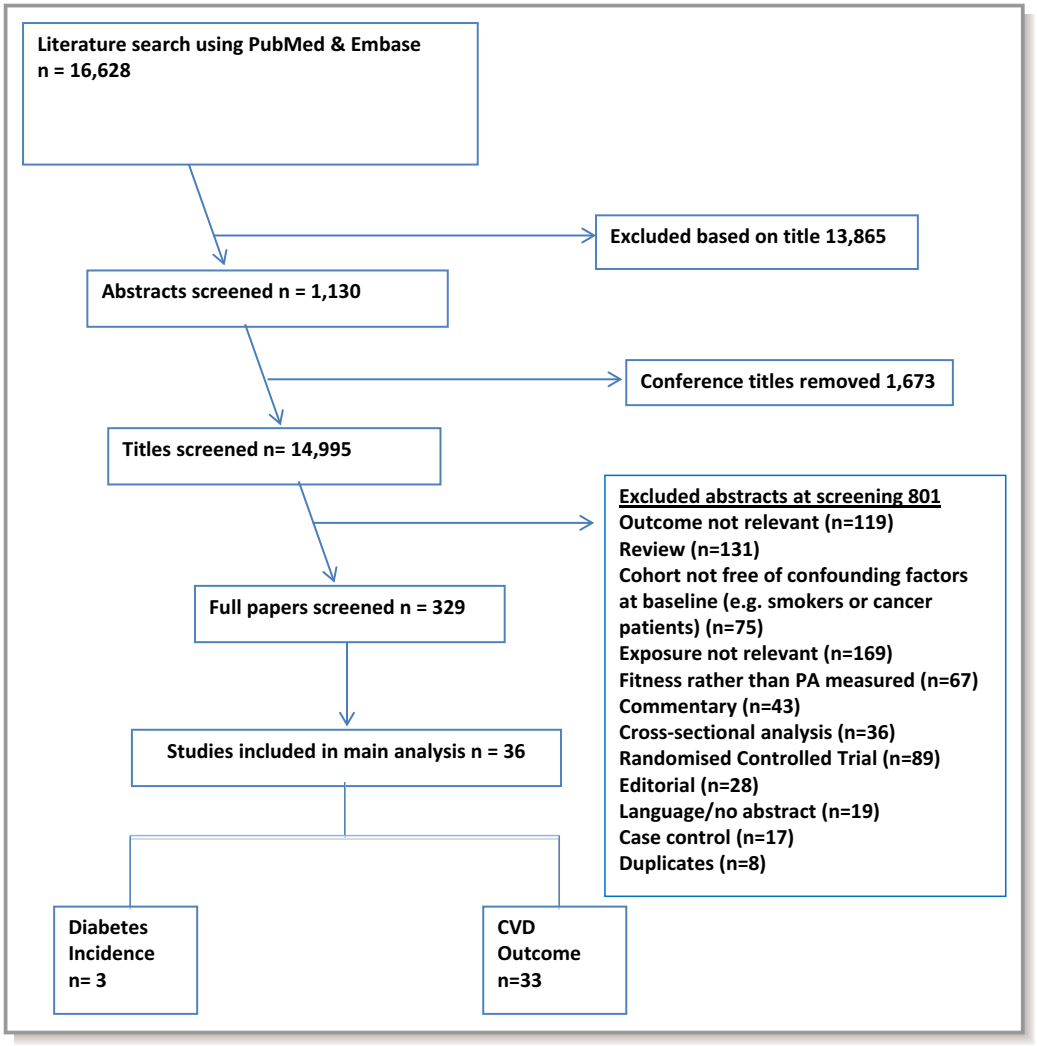

Figure 1. Flow chart for inclusion of studies. CVD indicates cardiovascular disease; diabetes, diabetes mellitus.

inactive to moderate PA. Therefore, one can extrapolate that the greatest benefit may be derived from an additional 6 MET h/week, with a risk reduction of ≈4.3% per MET h/week for CVD mortality and 1.7% for CVD incidence, respectively.

Type 2 Diabetes Mellitus

Three studies were identified with incidence of T2DM as an outcome variable. These 3 studies were conducted in the UK, United States, and China, respectively. They included a total of 261 618 participants and 19 417 events occurring during an average follow-up period of 7.5 years.

The meta-analysis found a 0.74 RR (95% CI, 0.77–0.72) for T2DM after adjustment for body weight and a marginally greater reduction in risk in models not adjusted for body weight.

The dose-response curve shown in Figure S10 demonstrates that the largest benefit may be derived when moving from inactive (0 METs) to 6 METs (RR, 0.77), compared with 0.74 in response to 11.25 MET h/week of PA as per current guidelines.

Sensitivity Analysis

For T2DM, CVD mortality, and CVD incidence, the results of the meta-analysis were robust to the method of parameterizing the dose-response relationship (Table 4). In general, the results obtained using the selected 0.25 transformation were similar to those obtained using other transformation for each of the disease outcomes, including both linear and log linear relationships. For CVD incidence, CVD mortality, stroke incidence, CHD incidence, CHD mortality, heart failure incidence, and MI incidence, the 0.25 power transformation produced the result furthest from the null hypothesis. For instance, in estimating the RR of CVD incidence for an

Table 2. Meta-Analysis Results for Effect of Increase in Physical Activity Equivalent to Moving From Inactivity to Achieving Current Recommendations (11.25 MET h/week, for CVD Incidence and Mortality and T2DM Incidence—Assuming a 0.25 Power Transformation

Condition (ICD-10 Code)	No. of Contributing Studies	Total No. of Events	Adjusted for Body Weight		Not Adjusted for Body Weight	
			RR (95% CI)	I^2	RR (95% CI)	I^2
CVD incidence (I00–I99)	5	6945	0.83 (0.77, 0.89)	0.0%	0.79 (0.72, 0.87)	33.3%
CVD mortality (I00–I99)	14	39 708	0.77 (0.71, 0.84)	73.6%	0.66 (0.52, 0.84)	93.6%
Stroke incidence (I60–I69)	9	13 599	0.82 (0.77, 0.87)	0.0%	0.78 (0.69, 0.88)	3.1%
CHD incidence (I20–I25)	6	12 655	0.80 (0.75, 0.86)	0.0%	0.77 (0.71, 0.83)	0.0%
CHD mortality (I20–25)	2	1022	0.80 (0.58, 1.09)	59.1%	n/a	n/a
Heart failure incidence (I50)	5	9457	0.81 (0.76, 0.86)	0.0%	0.75 (0.69, 0.82)	0.0%
MI incidence (I21–22)	2	6445	0.75 (0.62, 0.89)	0.0%	n/a	n/a
T2DM incidence (E11)	3	19 417	0.74 (0.72, 0.77)	0.0%	0.73 (0.68, 0.79)	56.0%

The various power transformations, namely, both linear and log linear associations, as well as power transformations of 0.25, 0.375, 0.50, and 0.75, are presented in Table 4 for the various outcomes. CHD indicates coronary heart disease; CVD, cardiovascular disease; ICD, International Classification of Disease; MI, myocardial infarction; RR, relative risk; n/a, too few studies for a meta-analysis; T2DM, type 2 diabetes mellitus.

11.25 MET h/week, increase in PA ranged from 0.83 (0.25 power transformation), versus RR 0.89 (0.75 power transformation) and 0.92 (linear transformation).

Uniquely, however, for T2DM incidence, the 0.25 power transformation produced a lower RR estimate as compared with the other transformations. For 0.25, the RR was 0.74, compared with a RR of 0.70 for the 0.75 transform and 0.68 for the linear relationship.

Estimates of relative risk for CHD incidence and heart failure incidence were more sensitive to the choice of parameterization, with results for CHD incidence ranging from RR 0.80 (0.25 power transformation) to 0.90 (linear relationship).

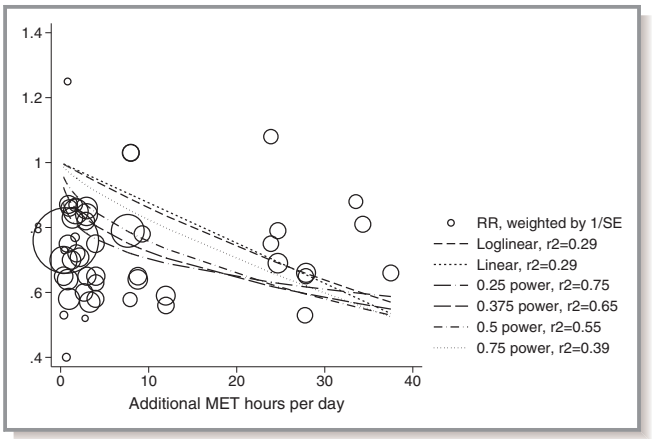

Figure 2. Relative risk for CVD mortality against MET hours per day. Results from 14 studies, including the 0.25 power transformation fit line as well as linear, log-linear, 0.375, 0.5, and 0.750 power transformations. Relative risk estimates are weighted by the inverse of the reported SE, with larger circles for results with greater weighting. The red line represents a log-linear transformation, and the orange line represents a 0.25 power transformation. CVD indicates cardiovascular disease; MET, metabolic equivalent of task; RR, relative risk.

Table S5 demonstrates the effects of limiting the meta-analyses to those studies that achieved at least 6 of the 8 quality criteria. This restriction made very little difference to the results, with a slight increase in the observed RR reduction associated with an 11.25 MET h/week increase in PA for the vast majority of disease outcomes. Interestingly, for CHD incidence, the RR reduction attenuated slightly from 0.23 to 0.19 when including only the higher-quality studies. As expected, however, there was some sensitivity when the quality criterion was used as a continuous measure, in that the very-low-quality studies overestimated the impact of PA on health.

A further sensitivity analysis was conducted to exclude studies with PA levels that were deemed implausible (ie, PA levels that were excessively high or low). The thresholds for implausibility were PA levels exceeding 10 times the recommendations, or lower than 30 minutes of PA per week, respectively (a level too low to be accurately measured by questionnaire). For CVD mortality, only 3 of 17 studies exceeded the maximum threshold, and only 1 study was under the minimum threshold (ie, recommended PA levels of 11.25 METs; Figure S11). However, Table S5 demonstrates that repeating the analysis without these implausible studies made negligible difference to the overall results. The highest level of PA in most CVD studies was around 2 to 3 times the recommended 11.25 MET h/week (Figure S12). The T2DM studies all had plausible PA-level ranges, as demonstrated in Figure S13. The highest exposure category had PA levels varying from 8.25 to 13.8 METs, corresponding well to the recommended PA levels of 11.25 METs/week.

Table 3. Categorical Analyses of Dose-Response Relationship of Physical Activity on CVD and T2DM, Compared to Baseline of Inactive Behaviour

Health Outcome	Low Physical Activity (0.1–11.5 METs h/week)	Medium Physical Activity (11.5–29.5 METs h/week)	High Physical Activity (29.5+ METs h/week)
CVD incidence (I00–I99)	0.89 (0.82, 0.98)	0.79 (0.69, 0.89)	0.75 (0.64, 0.87)
CVD mortality (I00–I99)	0.72 (0.67, 0.77)	0.72 (0.66, 0.78)	0.73 (0.67, 0.79)
Stroke incidence (I60–I69)	0.85 (0.80, 0.91)	0.81 (0.74, 0.88)	0.76 (0.68, 0.85)
CHD incidence (I20–I25)	0.87 (0.80, 0.95)	0.78 (0.74, 0.82)	0.70 (0.66, 0.75)
CHD mortality (I20–25)	N/A	0.76 (0.63, 0.93)	N/A
Heart failure incidence (I50)	N/A	0.79 (0.72, 0.85)	0.74 (0.68, 0.79)
MI incidence (I21–22)	N/A	0.76 (0.66, 0.87)	N/A
T2DM incidence (E11)	0.77 (0.74, 0.80)	0.70 (0.54, 0.90)	N/A

CHD indicates coronary heart disease; CVD, cardiovascular disease; MET, metabolic equivalent of task; MI, myocardial infarction; N/A, not available; T2DM, type 2 diabetes mellitus.

Heterogeneity and Assessment of Bias

Heterogeneity was demonstrated through the I^2 statistics and examination of both the forest and funnel plots. Table 2 demonstrated significant heterogeneity in the study results for CVD and CHD mortality, which may well be a consequence of the varying populations with differing baseline measures of PA and varying methods of measurement. Of note, however, inclusion of body-weight–adjusted studies did reduce the I^2 statistics throughout.

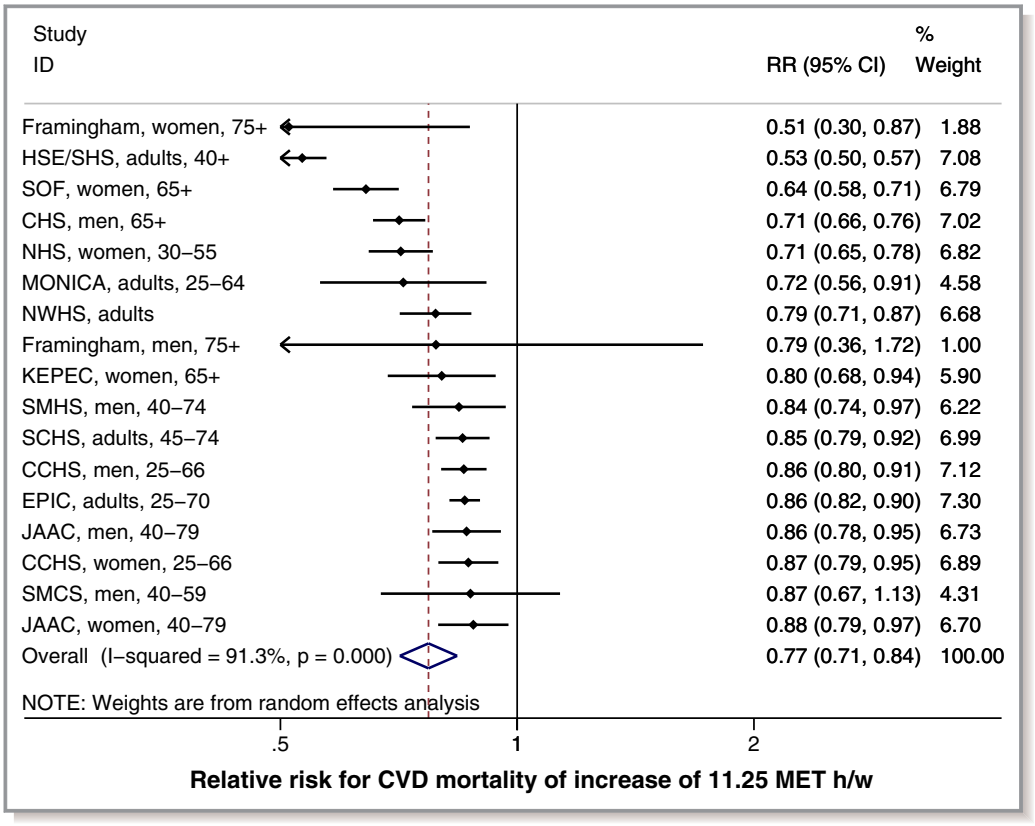

Figure 3. Meta-analysis of 11.25 MET h/week increase in physical activity on CVD mortality, with a 0.25 power transformation, adjusted for body weight. CVD indicates cardiovascular disease; MET, metabolic equivalent of task; RR, relative risk.

Table 4. Meta-Analysis Results for 11.25 MET h/week Increase on CVD and T2DM: Sensitivity to Transformation Assumptions

Health Outcome (ICD-10 Code)	RR for 11.25 MET h/week Increase in PA, With 95% CIs					
	0.25 Power	0.375 Power	0.5 Power	0.75 Power	Linear	Log Linear
CVD incidence (I00–I99)	0.83 (0.77, 0.89)	0.85 (0.79, 0.91)	0.86 (0.80, 0.92)	0.89 (0.83, 0.96)	0.92 (0.86, 0.98)	0.91 (0.85, 0.97)
CVD mortality (I00–I99)	0.77 (0.71, 0.84)	0.78 (0.70, 0.87)	0.79 (0.70, 0.90)	0.80 (0.67, 0.95)	0.80 (0.63, 1.01)	0.82 (0.70, 0.95)
Stroke incidence (I60–I69)	0.82 (0.77, 0.87)	0.82 (0.77, 0.87)	0.82 (0.77, 0.88)	0.84 (0.77, 0.91)	0.85 (0.77, 0.94)	0.85 (0.77, 0.93)
CHD incidence (I20–I25)	0.80 (0.75, 0.86)	0.82 (0.77, 0.88)	0.84 (0.79, 0.90)	0.88 (0.82, 0.93)	0.90 (0.85, 0.96)	0.89 (0.84, 0.95)
CHD mortality (I20–25)	0.80 (0.58, 1.09)	0.81 (0.61, 1.08)	0.82 (0.63, 1.07)	0.84 (0.67, 1.05)	0.86 (0.70, 1.05)	0.85 (0.68, 1.06)
Heart failure incidence (I50)	0.81 (0.76, 0.86)	0.83 (0.79, 0.89)	0.86 (0.81, 0.91)	0.89 (0.84, 0.95)	0.92 (0.87, 0.98)	0.91 (0.86, 0.97)
MI incidence (I21–22)	0.75 (0.62, 0.89)	0.76 (0.63, 0.91)	0.77 (0.65, 0.93)	0.81 (0.67, 0.97)	0.84 (0.70, 1.00)	0.83 (0.69, 0.99)
T2DM incidence (E11)	0.74 (0.72, 0.77)	0.73 (0.71, 0.76)	0.72 (0.70, 0.75)	0.70 (0.68, 0.72)	0.68 (0.66, 0.70)	0.69 (0.67, 0.71)

CHD indicates coronary heart disease; CVD, cardiovascular disease; ICD, International Classification of Disease; MET, metabolic equivalent of task; MI, myocardial infarction; PA, physical activity; RR, relative risk; T2DM, type 2 diabetes mellitus.

Examination of the forest plot for CVD mortality (Figure 3) revealed that both the Framingham[19] and the Health Survey for England[20] studies showed considerably larger effect sizes than the remaining studies. Metaregression was conducted to explore possible explanations of this heterogeneity.

Meta-Regression

Table S6 shows the effects of moderator variables on the RR of CVD mortality. First, there was an association between quality of study and effect size, with a metaregression coefficient of 0.07 per quality score point. In addition, it was noted that studies that measure body weight using subjective measurements estimate a 0.24 lower RR as compared with those that use objective measurements. In assessing the effects of geographical location, US cohort studies estimated an RR further from the null hypothesis, with a difference of ≈0.15, as compared with studies conducted elsewhere.

Small Study Bias or Publication Bias

Small study effects, or publication bias, was assessed through visual inspection of the funnel plots, as shown in Figure 4 for CVD mortality (the remaining conditions displayed in Figures S14 through S20). In general, the plots were highly symmetrical, showing little signs of publication bias. In certain disease outcomes, the smaller, less-powerful studies often overestimated the effects of PA. For example, in CVD incidence, the Framingham male cohort, which contributed a mere 0.4% weighting provided an RR estimate of 0.53 as compared with the overall estimated relative of CVD incidence of 0.83.

In contrast, however, for CHD incidence, the smallest study reported an increase in disease outcome for increasing PA levels. The Belstress men's cohort,[21] which was afforded a weighting of 0.50% reported an RR of 1.12 compared with the overall RR estimate of 0.80 for CHD incidence. These data points highlighted the effect of small study bias, which could be attributed to clinical or methodological diversity.

Discussion

We found a decrease in the risk of all cardiovascular outcomes and diabetes mellitus incidence with increasing levels of PA. These RRs were only marginally attenuated when adjusting for a measure of body weight, suggesting that the majority of the health benefit that accrues from increasing PA is mediated by mechanisms beyond weight maintenance. Our findings suggest that an increase in 11.25 MET h/week for an inactive individual is associated with a reduction of risk for cardiovascular mortality by 23% and diabetes mellitus incidence by 26%, independent of body weight. This may

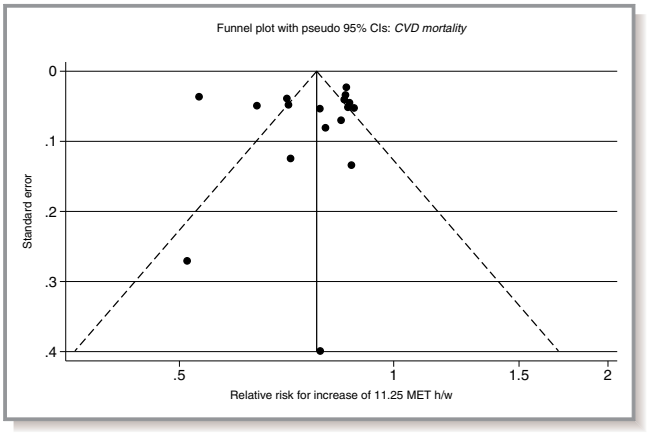

Figure 4. Funnel plot for meta-analyses of 11.25 MET h/week increase in physical activity, with a 0.25 power transformation, for CVD mortality, adjusted for body weight. CVD indicates cardiovascular disease; MET, metabolic equivalent of task.

provide greater effect sizes compared to more-recent studies, such as Arem et al.,[22] who used a value of 7.5 MET h/week; however, the key benefit of this article is that the results can be generated for an MET value, including 7.5 to provide a direct comparison.

Strengths and Weaknesses

This is the first meta-analysis to assess the effect of PA on CVD and diabetes mellitus using a continuous index of PA, thereby allowing for direct comparison of results across studies with heterogeneous data collection methods. Previous meta-analyses that have considered the effect of PA on health outcomes have mostly used categorical measures of PA (eg, high vs moderate vs low).[23–25] Those that used a single continuous comparable index of PA have not considered multiple health outcomes.[10,26–28] This study is the first to consider a range of CVDs simultaneously, allowing for comparable results across these disease boundaries.

The results of these meta-analyses, which can be used to estimate the risk reduction associated with a unit increase of PA at any PA level, are vital for an accurate assessment of the population burden of physical inactivity. A recent study estimated the global burden of physical inactivity and concluded that the population health burden associated with physical inactivity was of an equivalent size to that associated with smoking.[29] However, this analysis has been criticized for overestimating the burden of PA,[30] given that the researchers derived their population impact fractions (PIFs) for physical inactivity from RRs drawn from meta-analyses that either compare pooled estimates of "low" PA with "high" PA, or compare inactive behavior with meeting PA recommendations (although other assumptions by the authors are likely to result in underestimation).[29] The appropriate RRs for such PIFs should compare PA at the average level within the inactive population with the level required to meet recommendations. Such RRs can only be derived from analyses similar to those reported here, which account for the continuous nature of the PA variable.

Our results supported the assumption of other meta-analysis that the inactive have most to gain by any increase in PA. The relationship between PA and health outcomes is such that a small increase from inactive behavior provides most of the benefit, and subsequent increases produce diminishing returns. This is supported by 2 previous meta-analyses that assessed the dose-response relationship between PA and coronary heart disease[26] and all-cause mortality.[10] The Woodcock meta-analysis suggested that a first-degree fractional polynomial with 0.25 power (as has been used in this study) provides the best fit to the data.[10] However, a drawback of using such a transformation is that it is necessary to set a somewhat arbitrary "zero" level of PA. We assumed that the reference group from each of the studies achieved zero PA (ie, they were considered to be inactive), but the actual PA level in these groups will vary between studies. The fact that the included studies tended to show the same "diminishing returns" relationship with PA suggests that the levels of PA in the reference groups were fairly similar and approximately sedentary. However, this diminishing returns relationship could be evidence of a general bias present in the studies inflating the risk of disease in the PA reference groups. We explored the effect on meta-analysis results of method of parameterizing the dose-response relationship and also compared results with non-parametric categorical analyses and, in most cases, found that the results were robust to choice of method.

A limitation of using the comparable index of PA is that it does not distinguish between sustained periods of moderate activity and short periods of vigorous activity, which may have differing effects on health. Also, the PA recommendations[6] advise either 150 minutes of moderate-to-vigorous activity (150 MVPA) or 75 minutes of vigorous physical activity (75 VPA), whereas in this analysis we have focused on the more commonly used 150 MVPA. Therefore, our results pertain to 11.25 MET h/week, whereas for 75 VPA (with 6.5 METs for vigorous activity), the results would be presented for 9.75 MET h/week; therefore, this would attenuate the RR estimates. With respect to the search strategy, the potential of introducing bias into the review process by use of a single reviewer for reviewing full-text articles and for the data extraction process cannot be excluded, although a second reviewer cross-checked undecided cases and a 10% sample was checked by another reviewer at each stage of assessment.

The aim of this article was to explore the effect of total PA, expressed as metabolic expenditure, as opposed to domain-specific investigation. In reality, although many studies use a combination of domains to estimate total PA, they rarely truly include measurement of total PA exposure. We decided to include studies that had assessed 2 or more (of the 4 main) domains because this is likely to represent a reasonable minimum to be able to assess a meaningful proportion of overall PA exposure.

The studies included in this systematic review were mostly of high quality, notwithstanding the variability in PA measures. The prospective cohort study design provides some protection against recall or selection bias. There were few issues with loss to follow-up or with detection of events. However, the measures of PA used in the studies were heterogeneous, both in terms of the measurement tools and in the aspects of PA that were being measured. As a result, the derivation of the comparable index of PA was challenging and is likely to have included some misclassification bias, because we were forced to make assumptions about behavior and activity levels that were not reported in the studies. Usually, misclassification bias would result in an underestimate of effect size, but

Table 5. Comparison With Results From Other Meta-Analyses of the Effect of Physical Activity on CVD Outcomes Reported in Peer-Reviewed Journals

Citation	Health Outcome	Physical Activity Comparison	Relative Risk	95% CI	Studies Included in Meta-Analysis	Additional Notes
Oguma et al. (2004)[23]	CHD (incidence or mortality)	Categorical: moderate vs low	0.77	0.64 to 0.92	2	Includes case-control studies and retrospective cohort studies
		Categorical: high vs low	0.57	0.41 to 0.79		
Sofi et al. (2008)[33]	CHD (incidence or mortality)	Categorical: moderate vs low	0.88	0.83 to 0.93	22	Leisure time PA only
		Categorical: high vs low	0.73	0.66 to 0.80		
Diep et al. (2010)[24]	Stroke (incidence or mortality)	Categorical: high vs moderate vs low	0.81 0.89	0.75 to 0.87 0.86 to 0.93	13	
Jeon et al. (2007)[11]	T2DM incidence	Categorical: moderate vs sedentary	0.69	0.58 to 83	5	Not adjusted for body weight
Arem et al. (2015)[22]	CVD mortality	Categorial: low (0.1–7.5 METs)	0.80	0.77 to 0.84	6	Adjusted for body weight
		Categorial: low (0.1–7.5 METs)	0.67	0.65 to 0.80		

CHD indicates coronary heart disease; CVD, cardiovascular disease; MET, metabolic equivalent of task; PA, physical activity; T2DM, type 2 diabetes mellitus.

here it may have led to a reduction in variance in PA levels, which will have led to a general bias away from the null hypothesis for the studies included in the meta-analysis.

It has previously been noted that studies of the effect of PA on health would benefit from improved measures of non-leisure time PA, particularly for studying the effect in women where levels of recreational activity are lower.[24] The use of self-reported PA questionnaires in all of the included studies is problematic, given that self-reported PA has been shown to have a low-to-moderate correlation with objective measures.[31] Furthermore, whereas all of the studies used healthy participants, only half included a "burn-out" period to reduce the risk of reverse causation. The lack of availability of studies conducted in low- and middle-income countries precludes our ability to assess the impact of increasing PA levels in these settings, where the burden of physical inactivity and non-communicable diseases is also high. Given that all of the studies included in the meta-analysis were observational, the potential for residual confounding from imprecise or unmeasured factors cannot be excluded from pooling. Although all of the studies adjusted for multiple potential confounding variables, not all confounders were adjusted for in every study. Similarly, all of the results included in the meta-analysis were based on analyses using measures of PA and body weight made at only 1 time point, which is likely to result in underestimates of the effect of PA on health.

Comparison With Other Studies

Three other reviews investigating the effects of PA on CVD are summarized in Table 5.[11,22–24,32]

Each review had different objectives and used different methods both to identify studies and combine results. The majority have chosen to combine risk estimates based on categorical measures of the exposure variable. We believe that our point estimates for the RR associated with CVD outcomes (increasing PA by 11.25 MET h/week) correspond most closely with comparisons between moderate and low levels of PA. Our estimated RR of 0.83 for congestive heart disease incidence is similar to estimates from meta-analyses by Sofi et al.[33] and Oguma et al.,[23] whereas our estimate for stroke incidence is of greater magnitude than that by Diep et al.[24] Our estimate for T2DM incidence is similar to that produced by Jeon et al.[11]

Our study results for CVD mortality also proved similar to Arem et al.,[22] which fell outside our search dates but was added later at the review stage. Arem et al. studied the effects of leisure time PA on all-cause and also CVD mortality and found a CVD mortality hazard ratio of 0.80 between 0.1 and 7.5 METs and 0.67 corresponding to 7.5 to 15 METs of leisure time PA. These estimates correspond extremely well with our estimates for CVD mortality at 11.25 METs, although the main focus of the Arem et al. article was to explore the potentially harmful effects of extremely high PA levels, up to 75 MET h/week.

Conclusions

This meta-analysis has provided an assessment of the health benefits for a unit increase in PA levels, both before and after adjustment for body weight. The methods used here enable direct comparison of the effect of PA on a range of CVDs and diabetes mellitus.

Future studies should investigate the effect of increasing PA levels in low- and middle-income countries. Further analysis of the effect of increasing PA on other health

behaviors, such as diet and smoking, and an analysis of the potential differences that may arise with age, ethnicity, and socioeconomic status, for example, is also warranted. This meta-analysis provides clear direction for policy makers that there may be greater gains for population health by targeting those who do very little PA. However, population-level approaches to improving PA are still likely to be effective at reducing the health burden attributed to physical inactivity if the protective effect of PA on health is observed at high as well as low PA levels.

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Disclosures

None.

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SUPPLEMENTAL MATERIAL

Table S1. Criteria for assessment of bias / study quality

1st Author	Year	Representativeness of cohort	Selection of non-exposed	Measurement of body weight	Measurement of physical activity	Response rate	Loss to follow-up	Reverse causality	Measurement of health outcomes	Quality score
Sherman(1)	1994	1	1	1	0	0	1	1	1	6
Sesso(2)	1999	1	1	0	1	1	0	1	0	5
Hu(3)	2000	1	1	0	0	0	1	1	1	5
Sesso(4)	2000	1	1	0	0	0	1	1	0	4
Gregg(5)	2003	1	1	1	1	0	1	1	0	6
Hu (NHS)(6)	2004	1	1	0	0	0	1	1	1	5
Hu (Finnish pop)(7)	2004	0	1	0	1	0	1	1	1	5
Franco(8)	2005	1	1	1	0	0	1	1	0	5
Myint(9)	2006	1	1	1	1	0	1	1	1	7
Hu(10)	2007	0	1	0	1	0	1	1	1	5
Hu(11)	2010	1	0	1	0	1	0	1	1	5
Eguchi (12)	2012	1	1	1	0	0	0	1	1	5
Odegaard(13)	2011	1	1	1	1	0	1	1	1	7
Petersen(14)	2012	1	1	1	1	0	1	1	1	7
Reis(15)	2011	1	1	1	0	0	0	1	0	4
Shi(16)	2013	1	1	1	1	1	0	1	1	7
Baceviciene(17)	2012	1	1	1	1	1	0	0	1	6
Clays(18)	2012	1	1	1	1	0	0	1	1	6
Holtermann(19)	2012	1	1	1	1	1	0	1	1	7
Jefferis(20)	2012	1	1	1	1	1	0	1	1	7
Kraigher-Krainer(21)	2013	1	1	0	1	0	1	1	1	6
Park(22)	2012	1	1	1	1	0	0	0	1	5
Chomistek(23)	2013	1	1	0	1	0	0	1	1	5
Gunnell(24)	2013	1	1	1	1	0	0	1	1	6
Holtermann(25)	2013	1	1	1	1	1	0	1	1	7
Jefferis(26)	2013	1	1	1	1	1	0	1	1	7
Kim(27)	2013	1	1	1	1	0	0	1	1	6
McDonnell(28)	2013	0	1	1	1	1	0	1	1	6
Patel(29)	2013	1	1	1	1	1	0	1	0	6
Soedamah(30)	2013	1	1	0	0	0	0	1	1	4
Vergnaud(31)	2013	1	1	1	1	1	0	1	1	7
Wang(32)	2013	1	1	1	1	1	0	1	1	7
Williams(16)	2013	1	0	1	1	0	1	1	1	6
Zhang, Q(29)	2013	1	1	1	0	1	0	1	1	6
Zhang, Y(29)	2013	1	1	1	1	1	0	1	1	7
Young(33)	2014	1	1	1	1	0	0	1	1	6

- *Representativeness of cohort (0 = no description or selected group of users (e.g. nurses), 1 = otherwise)*
- *Selection of non-exposed (0 = no description or drawn from different source than exposed, 1 = otherwise)*
- *Measurement of body weight (0 = no description or self report, 1 = otherwise)*
- *Measurement of physical activity (0 = no description or non-validated self report, 1 = otherwise)*
- *Response rate (0 = no description or less than 60%, 1 = otherwise)*
- *Loss to follow-up (0 = no description or greater than 5%, 1 = otherwise)*
- *Reverse causality (0 = no description or included participants with health outcome at baseline, 1 = otherwise)*
- *Measurement of health outcome (0 = no description or incidence measured by self report of doctor diagnosis, 1 = otherwise)*

Table S2. Converting physical activity measures to a standardised metric of 'Additional METh/d'

The single metric that we converted all the measures from the identified papers to was 'Additional MET hours per day' (or 'Additional METh/d'). This measure is a comparative measure, where the baseline group in each paper is arbitrarily assigned the value of zero and the extra physical activity in the other exposure groups is estimated as the amount of time spent in physical activity multiplied by the intensity of the physical activity, measured in METs (or 'metabolic equivalents'). METs are a standard measure used in physical activity research, which are an estimate of the intensity of physical activity compared to a baseline of 1 MET which is the intensity of sitting quietly. A standard compendium of MET values for many different activities can be found on the Compendium of Physical Activities Google Site.(34)

In order to develop the 'Additional METh/d' metric, it is necessary to estimate the METh/d for all of the reported physical activities described in each paper for each of the exposure groups, and then subtract the baseline METh/d from each of the groups. There were a number of standard rules that we applied for each paper, to remove subjectivity from the process. These rules were as follows:

1. When a paper uses a range to describe an exposure (e.g. 0-2 h/week walking) we used a point estimate which was the mid-point of the range.
2. When a paper uses an open category to describe an exposure we assume that the size of this category is the same as the closest equivalent exposure category and then calculate the median. For example, if a paper categorised walking as 0-2h/week; 2-4h/week; 4+ h/week, then we assume that the last exposure group is 4-6h/week and use the median value of 5h/week.
3. When physical activity is measured in 'occasions' or 'sessions' but no time is estimated, we assume that each occasion or session is half an hour.
4. When a paper describes physical activity in terms of intensity (rather than describing the actual activity that was performed) then we assume the following MET values: light intensity: 2.5 METs; moderate intensity: 4.5 METs; vigorous intensity: 6.5 METs. Ambiguous activities are assigned to either light, moderate or vigorous intensity levels – for example, 'exercise' or 'sport' are both categorised as vigorous.
5. Where the paper tries to measure amount of time spent in 'moderate or vigorous' physical activity but gives no information about the type of activity, we assume a MET value of 5.5.
6. Often papers categorised groups using an 'or' function. For example, an exposure group may consist of individuals who walk for at least 5 hours per week or exercise for at least two hours per week. In these instances, we assumed that any combination of these two activities is equally likely. So we calculated the METh/d for someone who only walks 5 hours per week, for someone who only exercises for two hours a week, and for someone who both walks for five hours a week AND exercises for two hours a week. We then calculated the average of the three measures, and assigned that value to the exposure group.
7. When a paper split groups into x-tiles of an exposure variable and provided estimates of mean and standard deviation of the exposure variable in the whole sample, we assumed that the exposure variable was log-normally distributed (unless otherwise stated in the paper) and then calculate the exposure variable for each of the x-tile variables from this assumed distribution.

Table S3. Identified studies evaluating the effect of physical activity on CVD outcome and Type II Diabetes Incidence with adjustment for body weight

1st Author (year)	Cohort name	Domains of PA measured	Disease outcome	Disease ascertainment	Population	Sample size	Number of events	Follow-up (years)	Adjustments
Baceviciene (2012)(17)	MONICA	Recreational; Active Travel; Household	CVD mortality	National Death Register	Lithuanian adults aged 25-64	2,643	150	12.6	Age, sex, education, study year, smoking, alcohol, BMI, hypertension, cholesterol, glucose, CHD, stroke
Chomistek (2013)(23)	WHI	Recreational; Active Travel	CHD incidence	Questionnaire & medical records, adjudicated by physicians	US women aged 50-79	71,018	2,411	12.2	Age, sedentary time, race, education, income, marital status, smoking, history of MI, depression, alcohol, sleep, total calories, saturated fat & fibre, BMI
			Stroke incidence				2,050		
			CVD incidence				4,235		
Clays (2012)(18)	Belstress	Recreational; Occupational	CHD incidence	Not reported	Belgian adults aged 35-59	14,337	87	3.15	Age, educational level, occupational class, job strain, BMI, smoking, alcohol, diabetes, SBP, cholesterol, HDL,
Eguchi (2012) (12)	JAAC	Recreational; Active Travel	CVD mortality	Death Certificates	Japanese men aged 40-79	18,747	441	16.5	Age, hx of hypertension, hx of diabetes, education, employment, mental stress, seven health behaviours (fruit, fish, milk, exercise, BMI, ethanol, sleep, smoking)
					Japanese women aged 40-79	24,263	408		
Franco (2005)(8)	Framingham	Recreational; Active Travel; Household; Occupational	CVD incidence	Physician evaluation of diagnosis	US adults aged 28-62,	9,033	1,573	12.0	Age, sex, smoking, BMI, hypertension, co-morbidities

1st Author (year)	Cohort name	Domains of PA measured	Disease outcome	Disease ascertainment	Population	Sample size	Number of events	Follow-up (years)	Adjustments
Gregg (2003)(5)	SOF	Walking; leisure activities; sports	CVD mortality	Death certificates	US women aged >65	9,518	826	10.6	Age, smoking, BMI, co-morbidities
Gunnell (2013)(24)	HWSS	Recreational; Active Travel	IHD disease incidence	Hospital records	Australian adults aged >45	14,890	538	3	Age, sex, smoking, charlson index, LTPA, sedentary activity level, BMI, fruit & veg intake, survey year, diabetes hospitalisation
Holtermann (2012)(19)	Copenhagen City Heart Study	Recreational; Household	IHD mortality	Death registry	Danish men aged 40-59	5,249	579	30	Age, clinical factors (BMI, BP)
Holtermann (2013)(25)	Copenhagen City Heart Study	Recreational; Occupational	CVD mortality	National Death Register	Danish men aged 25-66	7,411	1,945	22.4	Age, smoking, alcohol, cholesterol, SBP, blood pressure meds, diabetes, household income, BMI
					Danish women aged 25-66	8,916	1,814	22.4	
Hu (2000)(3)	Nurses Health Study	Walking; vigorous exercise activities	Stroke incidence	Self-report and health screening	US women aged 40-65	72,488	407	8.0	Age, smoking, BMI, alcohol, menopausal status, parental history of CHD, aspirin use, co-morbidities
Hu (2004)(6)	Nurses Health Study	Walking; leisure activities	CVD mortality	Death certificates	US women aged 30-55	116,564	2,370	24.0	Age, BMI, smoking, alcohol, parental history of CHD, menopausal status, hormone use
Hu (2004)(7)	Finland population	Occupational PA; leisure activities	CVD incidence	Routine update from registry	Finnish adults aged 25-64	18,892	818	9.8	Age, education, alcohol, smoking, BMI, SBP, cholesterol, co-morbidities

1st Author (year)	Cohort name	Domains of PA measured	Disease outcome	Disease ascertainment	Population	Sample size	Number of events	Follow-up (years)	Adjustments
Hu (2007)(10)	Finland population	Occupational PA; active travel; leisure activities	CHD incidence	Routine update from registry	Finnish adults aged 25-64	47,840	4,660	18.9	Age, education, alcohol, smoking, BMI, SBP, cholesterol, diabetes
Hu (2010)(11)	Finland population	Occupational PA; active travel; leisure activities	Heart Failure incidence	Routine update from registry	Finnish adults aged 25-74	59,178	3,614	18.4	Age, education, alcohol, smoking, BMI, SBP, cholesterol, co-morbidities
Jefferis (2012)(20)	BRHS	Recreational; Active Travel; Household	Type II Diabetes incidence	Self report, then correspondence with primary care	UK men aged 60-79	2,675	113	7.1	Age, region, social class, smoking, alcohol, coffee, total kcal/day, dietary intake, cholesterol. BMI
Jefferis (2013)(35)	BRHS	Recreational; Household; Active Travel	Stroke incidence	NHS central registers & death certificates	UK men aged 40-59	3,435	195	10.9	Age, region, alcohol, smoking, social class, cholesterol, SBP, BMI, AF, LVH
Kim (2013)(27)	Seoul Male Cohort Study	Recreational; Active Travel; Household; Occupational	CVD mortality	Mortality microdata by National stats office	Korean adults aged 40-59	12,538	171	19	Age, educational attainment, alcohol, sleep, FHx of CVD, smoking, BMI, health score, cholesterol, blood pressure, glucose
Kraigher-Krainer (2013)(21)	Framingham	Recreational; Occupational	Heart Failure Incidence	Review of medical records & adjudicated by physician panel	US adults aged 30-62	1,142	250	10	Age, sex, SBP, Hypertension, diabetes, valve disease, alcohol, LV hypertrophy, BMI

1st Author (year)	Cohort name	Domains of PA measured	Disease outcome	Disease ascertainment	Population	Sample size	Number of events	Follow-up (years)	Adjustments
McDonnell (2013)(28)	REGARDS	Recreational; Occupational; Active Travel	Stroke incidence	Patients, medical records and adjudication by 2 physicians	US adults aged >45	27,348	918	5.7	Age, sex, race, age-race interaction, socioeconomic factors, diabetes, hypertension, BMI, alcohol, smoking
Myint (2006)(9)	EPIC - Norfolk	Occupational PA; leisure activities	Stroke incidence	Routine update from registry	UK adults aged 40-79	20,040	361	8.6	Age, sex, BMI, SBP, cholesterol, smoking, alcohol, diabetes
Odegaard (2011)(13)	Singapore Chinese Health Study	Recreational; Active Travel	CVD mortality	Registries	Chinese adults aged 45-74	44,056	1,971	13	Factors simultaneously (BMI, Alcohol, Smoking, Diet, sleep), Age, sex, dialect, age enrolled, education, diabetes, FHx of Colorectcal Ca, energy intake
Park (2012)(22)	KEPEC	Recreational; Household	CVD mortality	Death Certificates	Korean women aged >65	5,079	607	8	Age, self-reported health, self-reported limitation in activity, smoking status, drinking status, body mass index, religion and other types of physical activity
Patel (2013)(29)	CHS	Recreational; Occupational; Household; Active Travel	Heart Failure incidence	Adjudicated by CHS Events committee	US adults aged >65	5,503	1,037	13	Age, sex, race, education, income, alcohol, smoking, BMI, Coronary artery disease, MI, Hypertension, T2DM, Stroke,
			Acute MI incidence				5,061		
			Stroke incidence				5,290		

1st Author (year)	Cohort name	Domains of PA measured	Disease outcome	Disease ascertainment	Population	Sample size	Number of events	Follow-up (years)	Adjustments
Petersen (2012)(14)	Copenhagen City Heart Study	Recreational; Active Travel	CVD mortality	National patient register			877	13	Age, education, smoking habits, alcohol, BMI, diabetes, cholesterol, blood pressure lowering therapy
			CHD incidence		Danish men aged 20-93	4,487	1431		
			MI incidence				795		
			CHD incidence		Danish women aged 20-93	5,956	1,393		
			MI incidence				589		
Reis (2011)(15)	NIH-AARP	Occupational; Household	Type II Diabetes	Self-report	US men aged 50-71	114,996	11,031	10	Age, Race, educational attainment, marital status, BMI, diet, Alcohol, smoking
					US women aged 50-71	92,483	6,969		
Sesso (1999)(2)	CAHS	Walking; stair climbing; sports	CVD incidence	Self-report of doctor diagnosis	US women, 37-69	1,564	181	31	Age, BMI, SBP, smoking, family history of CHD, diabetes
Sesso (2000)(4)	Harvard college alumni	Walking; stair climbing; sports; leisure activities	CHD incidence	Self-report of doctor diagnosis	US adults aged 39-88	12,516	2,135	16.0	Age, BMI, smoking, alcohol, hypertension, diabetes, early parental death
Sherman (1994)(1)	Framingham	Recreational; Active Travel; Household; Occupational	CVD mortality	Death certificates	US adults >75	285	81	10.0	Age, SBP, cholesterol, smoking, weight, glucose intolerance, co-morbidities

1st Author (year)	Cohort name	Domains of PA measured	Disease outcome	Disease ascertainment	Population	Sample size	Number of events	Follow-up (years)	Adjustments
Shi (2013)(36)	SMHS	Recreational; Active Travel	Type II Diabetes	Follow-up surveys and checking if conforms to American guidelines	Chinese adults aged 40-64	51,464	1,304	5.4	Age, Energy intake, Smoking, Alcohol, education level, occupation, income level, hypertension, family history of diabetes, BMI, WHR
Soedamah (2013)(30)	Health Survey for England and Scottish Health Survey	Recreational; Household; Active Travel	CVD mortality	Patient-based database of deaths	UK adults aged >40	17,410	638	9.7	Age, Marital status, Social Class, Ethnicity, Education, Survey year, cigarette smoking status, longstanding illness, BMI, domestic activity and alcohol
Vergnaud (2013)(31)	EPIC	Recreational; Occupational; Household; Active Travel	CVD Mortality	Board of health & death indexes	Europeans Aged 25-70	378,864	23,828	12.8	Sex, Age, Centre, Educational level, smoking, menopause, body fatness, calorific foods, plant foods, animal foods, alcohol & breastfeeding
Wang (2013)(32)	SMHS	Recreational; Occupational; Household; Active Travel	CVD mortality	National patient register	Chinese men 40-74	61,477	1,181	5.48	Age, Educational level, Income, Occupation, alcohol, pack-years of smoking, energy intake, red meat, fruit, daily PA other than exercise, BMI, Hx of CVD, Diabetes, Hypertension, Liver disease
Williams (2013)(16)	NWHS	Recreational; Active Travel; Household; Occupational	CVD mortality Ischaemic Heart disease incidence	National death index	US walking magazine subscribers (ages unknown)	42,022	834 443	9.6	Age, race, sex, education, prior heart attack, aspirin use, intake of meat, fruit, alcohol, BMI and medication use

1st Author (year)	Cohort name	Domains of PA measured	Disease outcome	Disease ascertainment	Population	Sample size	Number of events	Follow-up (years)	Adjustments
Young (2014)(33)	California Men's Health Study	Recreational; Active Travel; Household; Occupational	Heart Failure Incidence	National patient register	US men aged 45-69	82,695	3,473	7.8	Age, race/ethnicity, education, income, BMI, smoking, hypertension, diabetes, anti-hypertensives, HDL, glucose, triglycerides, food intake, alcohol
Zhang, Q (2013)(29)	Kailuan	Recreational; Occupational; Household; Active Travel	Stroke incidence: total, ischaemic and haemorrhagic	2 yearly physician interviews and checking hospital discharges	Chinese adults aged 19-98	91698	1,486	4	Smoking, BMI, Diet, Cholesterol, Blood pressure, Glucose, Age, Sex, Hospital, Education, Income
Zhang, Y (2011)(37)	MONICA	Recreational; Occupational	Stroke incidence: total, ischaemic and haemorrhagic	Computer registry	Finnish adults Finnish adults aged 25-74	36,686	1,478	13.7	Age, Study year, sex, smoking, physical activity, vegetable consumption, fruit consumption, education, alcohol, FHx of Stroke, Hx of Diabetes, BMI, SBP, Cholesterol

AF – Atrial Fibrillation; BMI – Body Mass Index; BP – Blood pressure; BRHS – British Regional Heart Study; CAH - College Alumni Health Study; CHS – Cardiovascular Health Study; CHD – Coronary Heart Disease; CVD Cardiovascular disease; EPIC – European Prospective Investigation of Cancer; FHx – family history; HWSS – Health and Wellbeing Surveillance System; Hx – history; JAAC - Japan Collaborative Cohort Study; JPHC – Japan Public Health Center based prospective study; KEPEC – Korean Elderly Pharmacoepidemiologic Cohort; LTA - Leisure Time Physical Activity; LVH – Left Ventricular hypertrophy; MI – Myocardial Infarction; Monica – the WHO Multinational Monitoring of Trends and Determinants of Cardiovascular Disease; NHANES – National Health and Nutrition Examination Survey; NHS – National Health Service; NHS – Nurses' Health Study; NIH-AARP – National Institute of Health – American Association of Retired Persons; NWHS - National Walker's Health Study; PA – physical activity; REGARDS – Reasons for Geographic Differences in Stroke; SBP – Systolic Blood Pressure; SMHS - Shanghai Men's Health Study; SOF – Study of Osteoporotic Fractures; SOF – Study of Osteoporotic Fractures; T2DM Type II Diabetes Mellitus; US – United States; VTE – Venous thromboembolism; WHI – Women's Health Initiative; CHS – Cardiovascular Health Study; WHR - Waist-to-hip ratio

Table S4. Excluded studies and data points evaluating the effect of physical activity on CVD outcome and Type II Diabetes Incidence.

Note these studies have been excluded as only one data point for the disease outcome was found, therefore it was decided not to include in a meta-analysis

1st Author (year)	Cohort name	Domains of PA measured	Disease outcome	Disease ascertainment	Population	Sample size	Number of events	Follow-up (years)	Adjustments
Patel (2013)(29)	CHS	Recreational, Occupational, Household, Active Travel	Angina incidence	Adjudicated by CHS Events committee	Age >65	5,503	4708	13	Age, sex, race, education, income, alcohol, smoking, BMI, Coronary artery disease, Myocardial infarction, Hypertension, T2DM and Stroke
Williams (2013)(16)	NWHS	Recreational, Active Travel, Household, Occupational	Cerebrovascular disease mortality	National death index	Walking magazine subscribers	42,022	147	9.6	Age, race, sex, education, prior heart attack, aspirin use, intake of meat, fruit, alcohol, BMI and medication use
			Heart Failure mortality				53		
			Diabetes mortality				48		
Wattanakit (2012)(38)	ARIC	Recreational, occupational	Venous thromboembolism incidence	Telephoning patients & hospital discharge list	Adults aged 45-64	15340	468	15.5	BMI, age, race, field centre, and sex

ARIC – Atherosclerosis Risk in Communities Study; BMI – Body Mass Index; CHS – Cardiovascular Health Study; NWHS - National Walker's Health Study.

Table S5. Sensitivity analyses: results restricted to studies that achieved at least six of the eight study criteria; studies with implausible PA values removed. Meta-analyses adjusted for body weight for 11.25 METhr/week increase in PA, with a 0.25 power transformation

	High quality studies only		*Implausible PA ranges removed*		*Main results (for comparison)*	
Condition (ICD-10 code)	RR (95% CI)	I^2	RR (95% CI)	I^2	RR (95% CI)	I^2
CVD incidence (I00-I99)	*n/a*		0.83 (0.77, 0.89)	0.0%	0.83 (0.77, 0.89)	0.0%
CVD mortality (I00-I99)	0.81 (0.76, 0.86)	25.1%	0.76 (0.69, 0.84)	78.2%	0.77 (0.71, 0.84)	73.6%
Stroke incidence (I60-I69)	0.81 (0.75, 0.87)	0.0%	0.82 (0.77, 0.87)	0.0%	0.82 (0.77, 0.87)	0.0%
CHD incidence (I20-I25)	0.76 (0.67, 0.86)	0.0%	0.79 (0.74, 0.86)	0.0%	0.80 (0.75, 0.86)	0.0%
CHD mortality (I20-25)	0.80 (0.58, 1.09)	59.1%	0.80 (0.58, 1.09)	59.1%	0.80 (0.58, 1.09)	59.1%
Heart failure incidence (I50)	0.79 (0.73, 0.85)	0.0%	0.80 (0.75, 0.86)	4.0%	0.81 (0.76, 0.86)	0.0%
Myocardial infarction incidence (I21-22)	0.75 (0.62, 0.89)	0.0%	0.75 (0.62, 0.89)	0.0%	0.75 (0.62, 0.89)	0.0%
Type 2 diabetes incidence (E11)	0.71 (0.52, 0.97)	27.3%	0.74 (0.72, 0.77)	0.0%	0.74 (0.72, 0.77)	0.0%

n/a - too few studies for a meta-analysis

Table S6. Meta-regressions: Association between study-level variables and CVD mortality relative risk for 11.25 METhours/week increase in physical activity, assuming .025 power transformation

Study-level variables	*Meta-regression coefficient*	*p*
Quality score (minimum = 1; maximum = 8)	0.07	0.023
Method of obesity measurement (0 = subjective; 1 = objective)	0.24	0.001
Validated PA measurement (0 = no; 1 = yes)	0.07	0.342
Gender (0 = men only; 1 = women only)	-0.03	0.654
Mean age of participants (0 = under 65; 1 = 65+)	-0.09	0.287
Active travel (0 = not included; 1 = included)	-0.07	0.480
Occupational PA (0 = not included; 1 = included)	0.06	0.351
Household PA (0 = not included; 1 = included)	-0.07	0.330
Mean follow-up years	0.01	0.381
Geography (baseline – US): Europe	0.07	0.000
Geography (baseline – US): Other	0.15	0.000

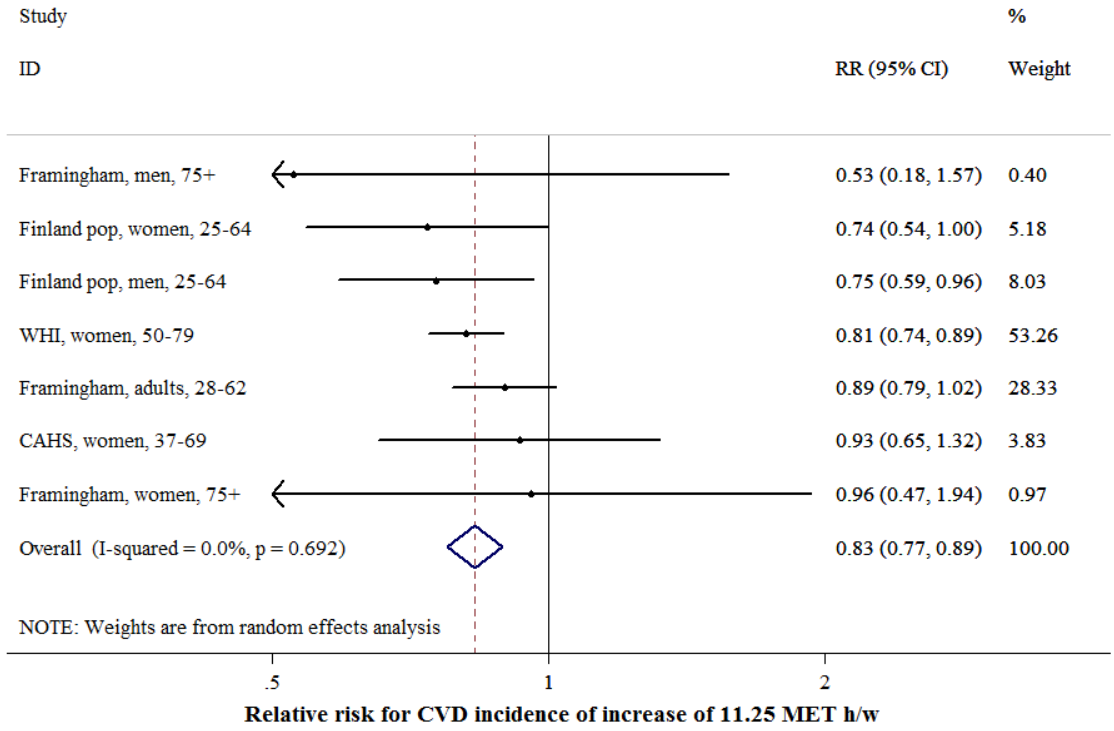
NB: CVD mortality selected as outcome as it has the most data lines (17 data lines from 14 studies) and considerable heterogeneity. Meta-regression weighted by the inverse of the standard error. Results are not mutually adjusted.

Supplemental Figures

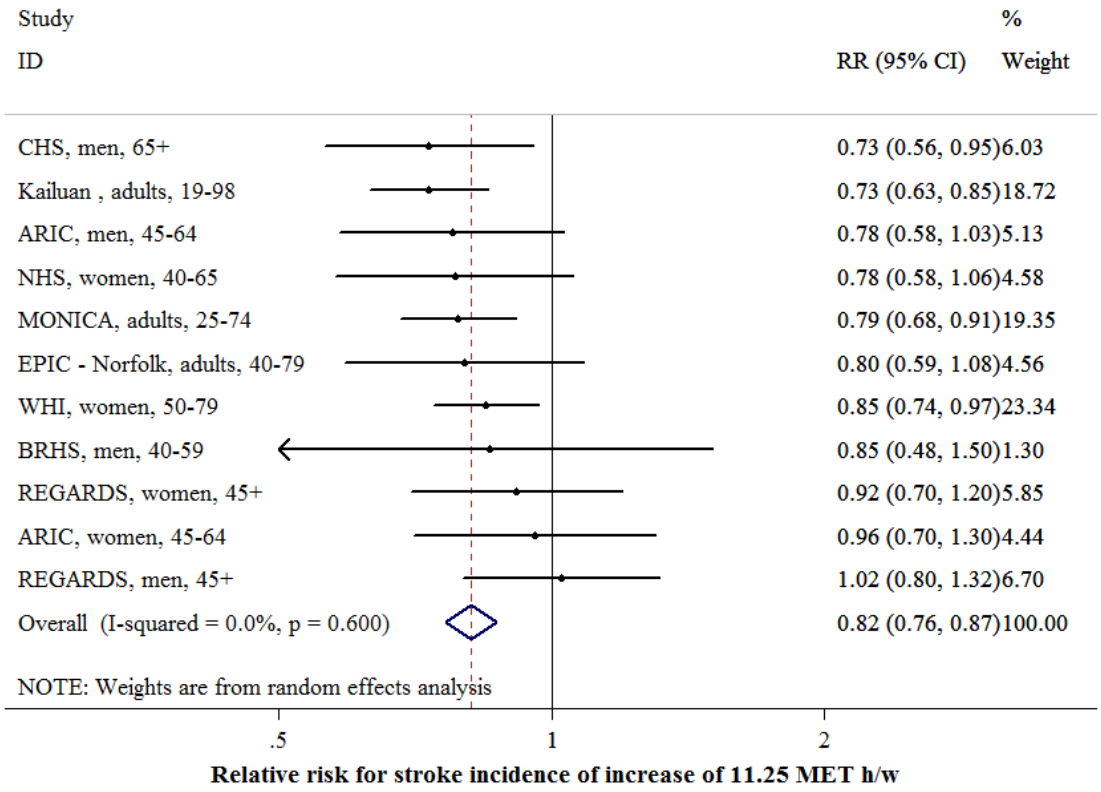
Figures S1-7: Meta-analysis of 11.25 METhr/week increase in physical activity for cardiovascular disease and diabetes health outcomes

Meta-analysis results are displayed for all the power 0.25 analyses, adjusted for body weight. Conditions are given in the figures.

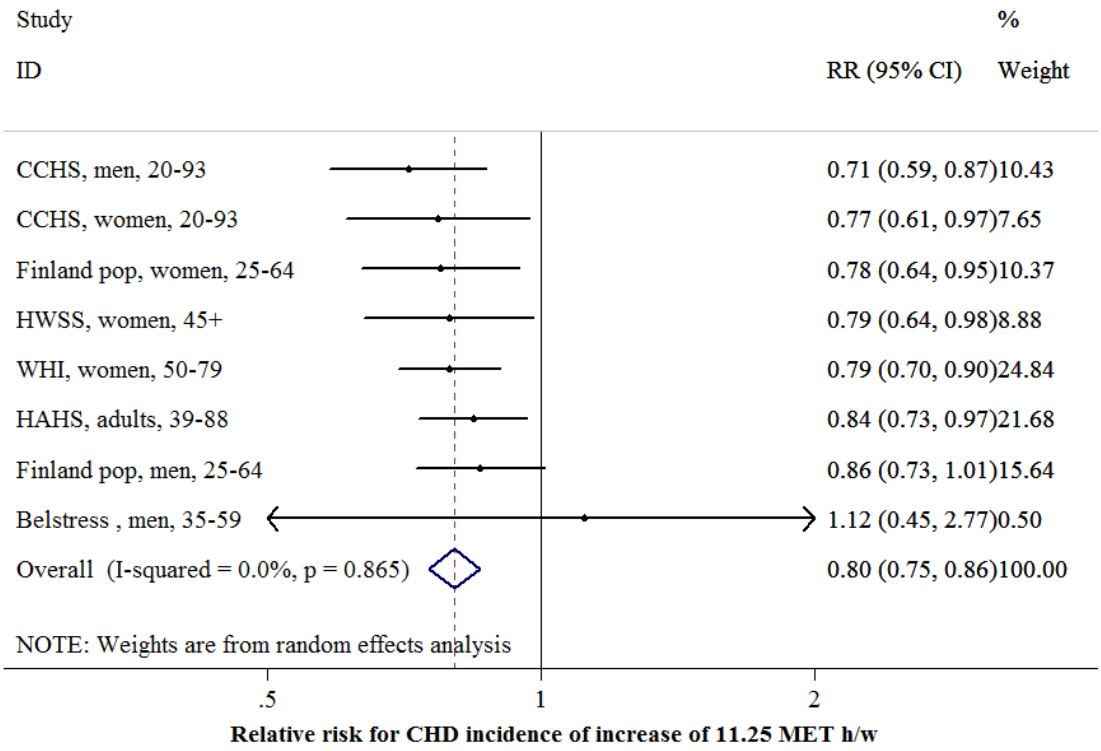
S1: CVD incidence



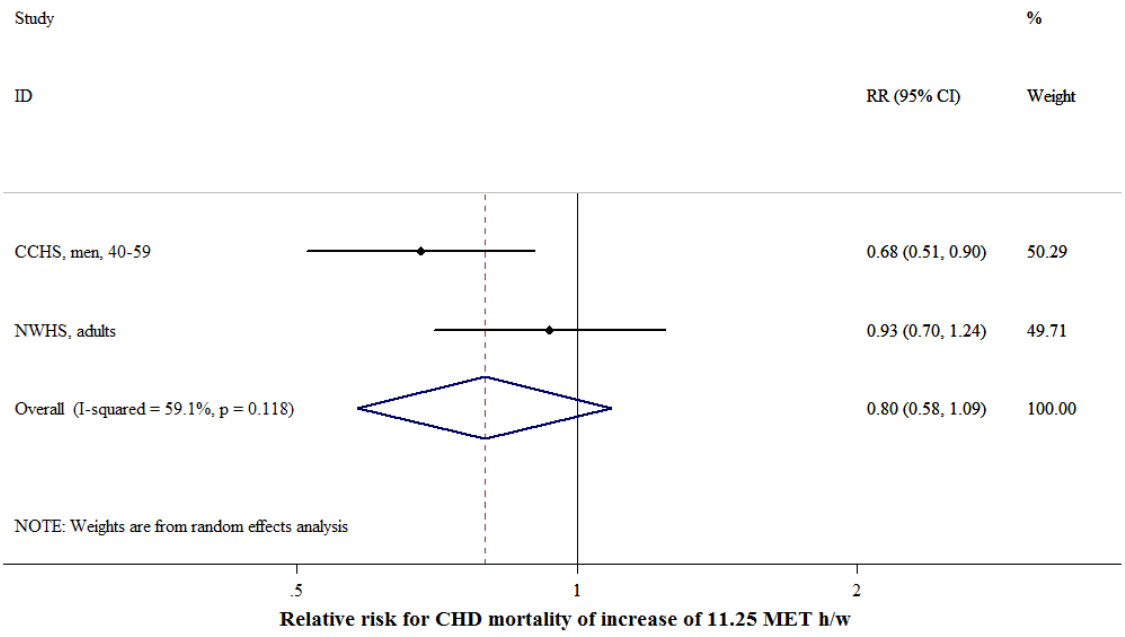
S2: Stroke incidence



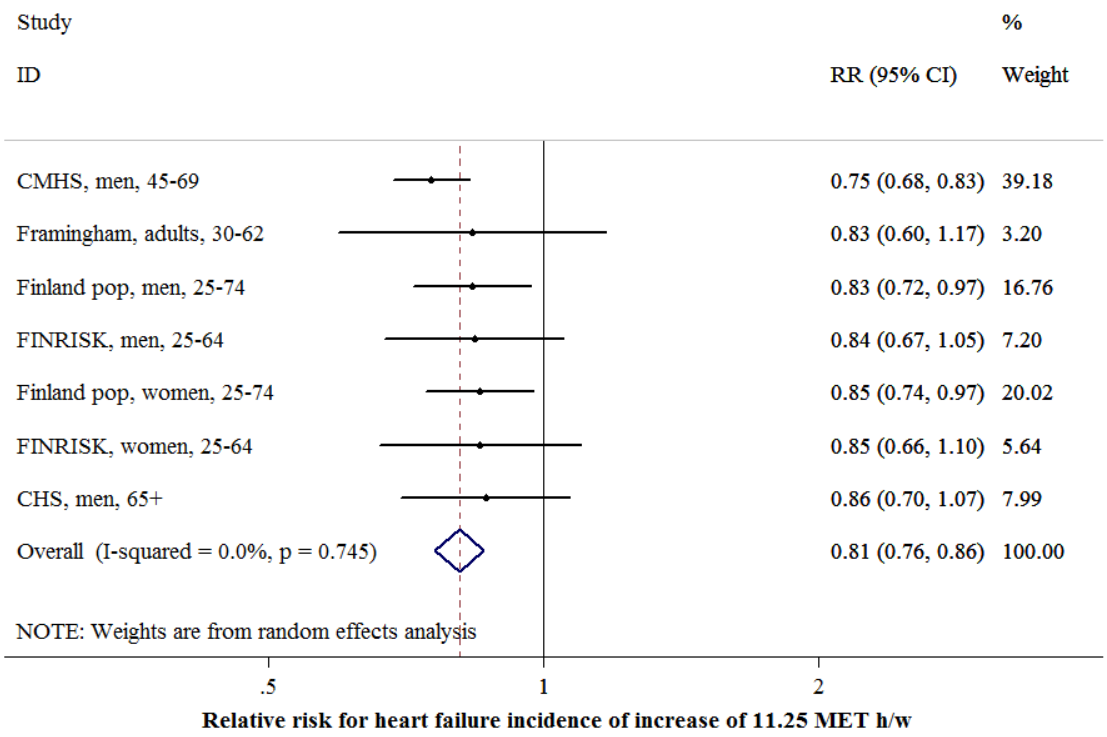
S3: CHD incidence



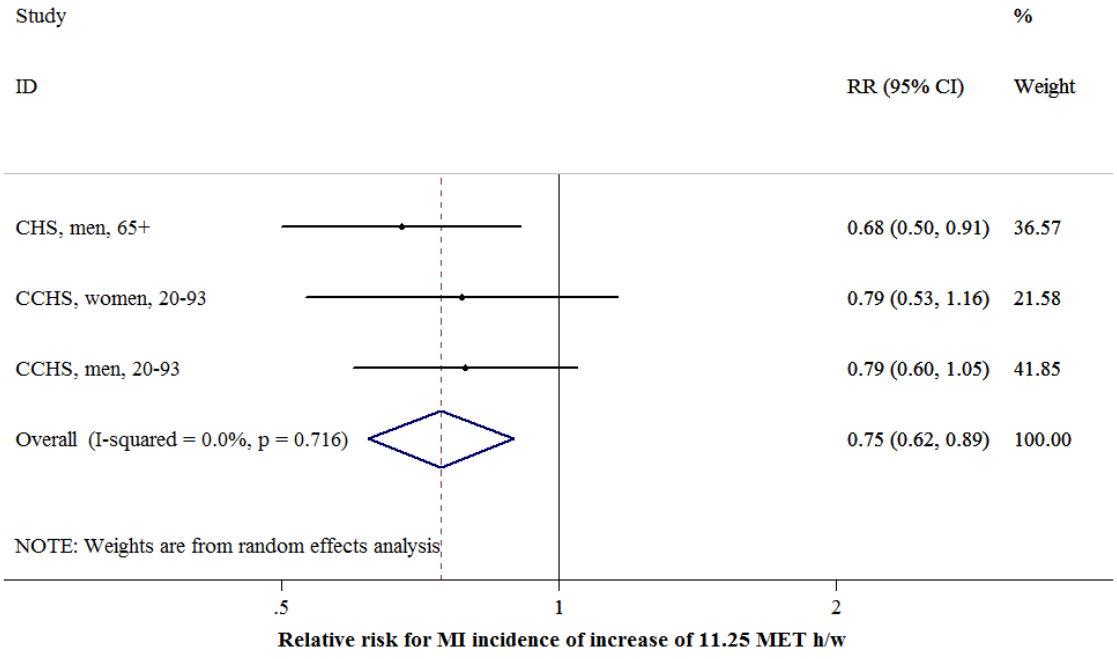
S4: CHD mortality



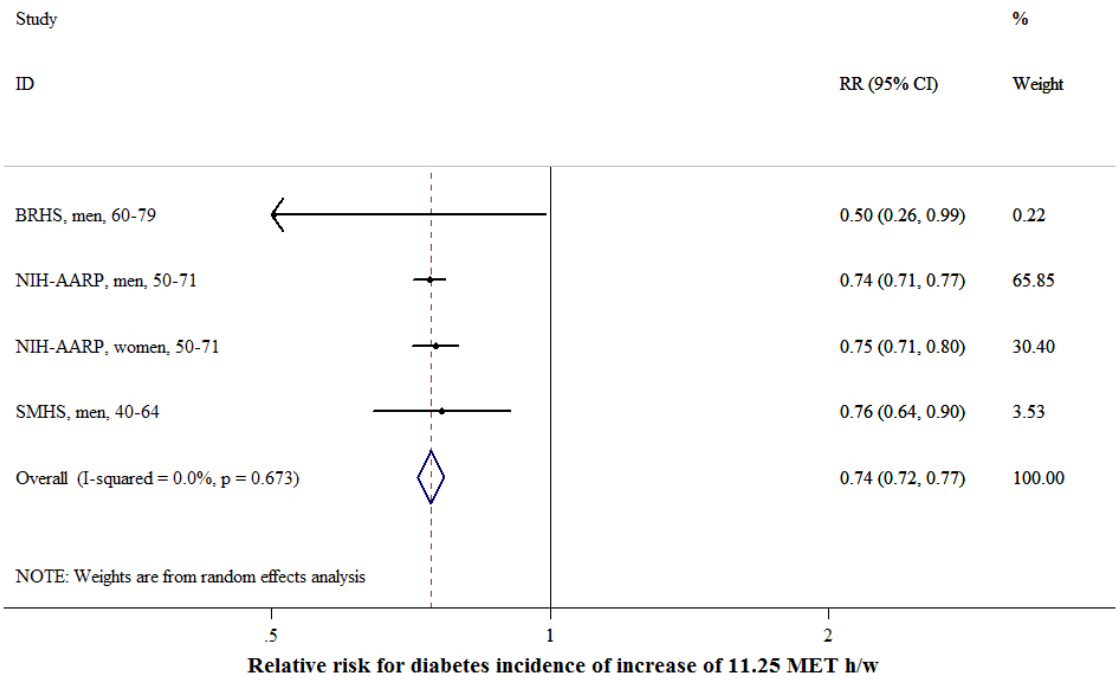
S5: Heart failure incidence



S6: MI incidence



S7: Diabetes incidence



Figures S8-S10: Dose-response relationship for the effect of 11.25 METhr/week increase in physical activity for the cardiovascular disease and diabetes health outcomes

Meta-analysis results are displayed for all the power 0.25 analyses, adjusted for body weight. Conditions are given in the figures.

Figure S8: CVD mortality

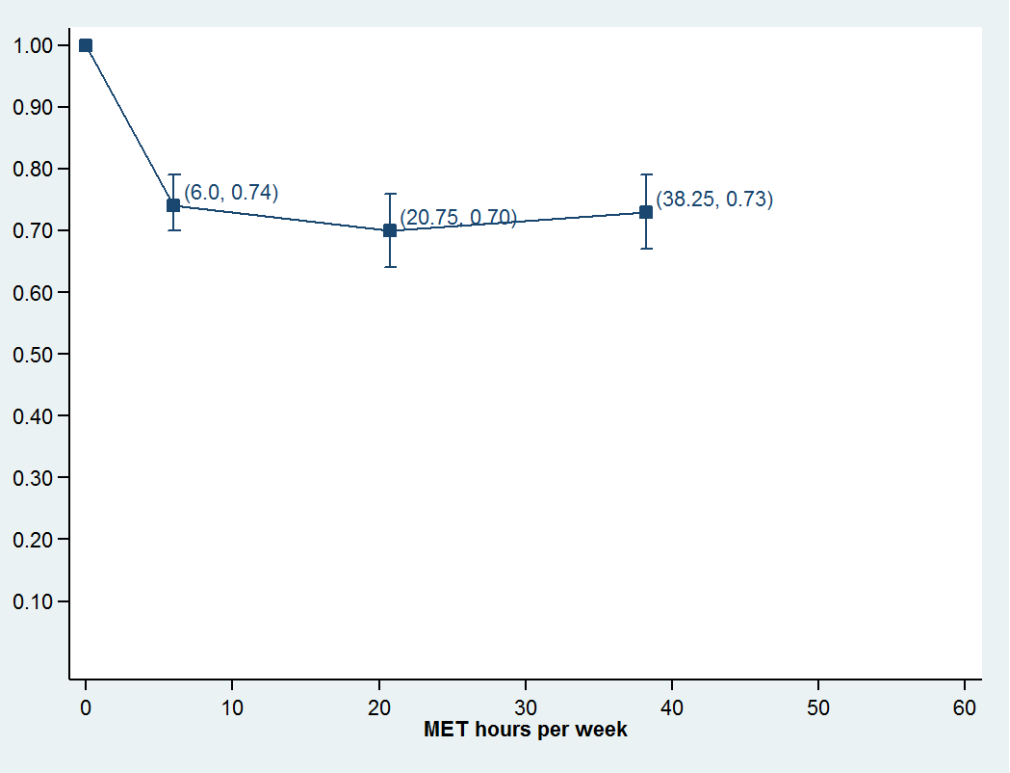


Figure S9: CVD incidence

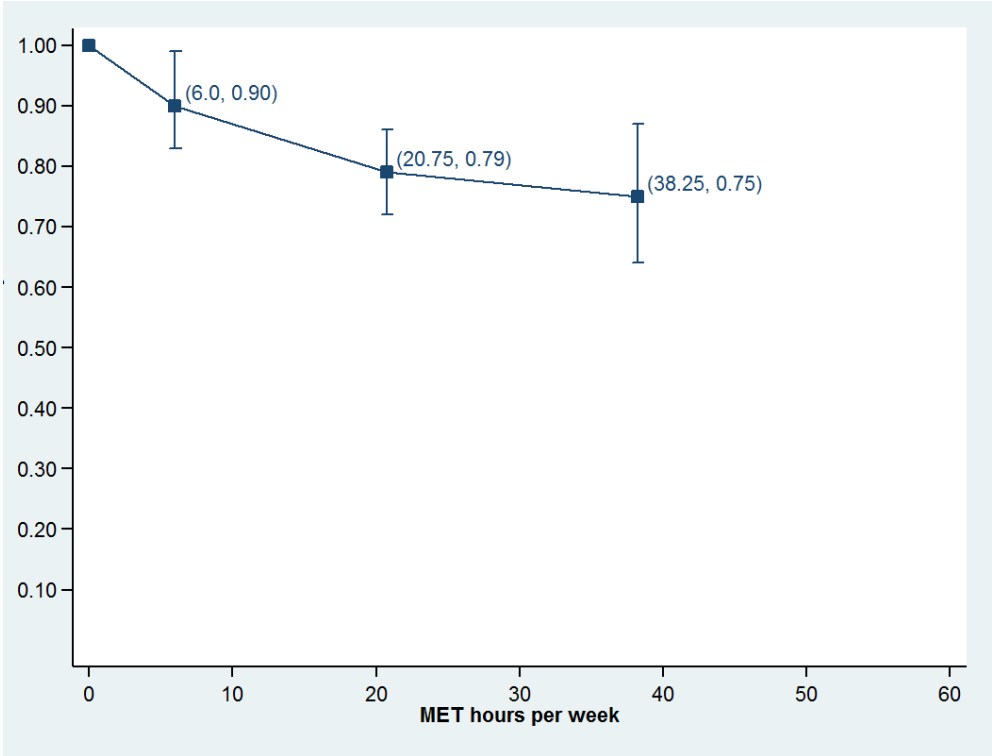


Figure S10: T2DM incidence

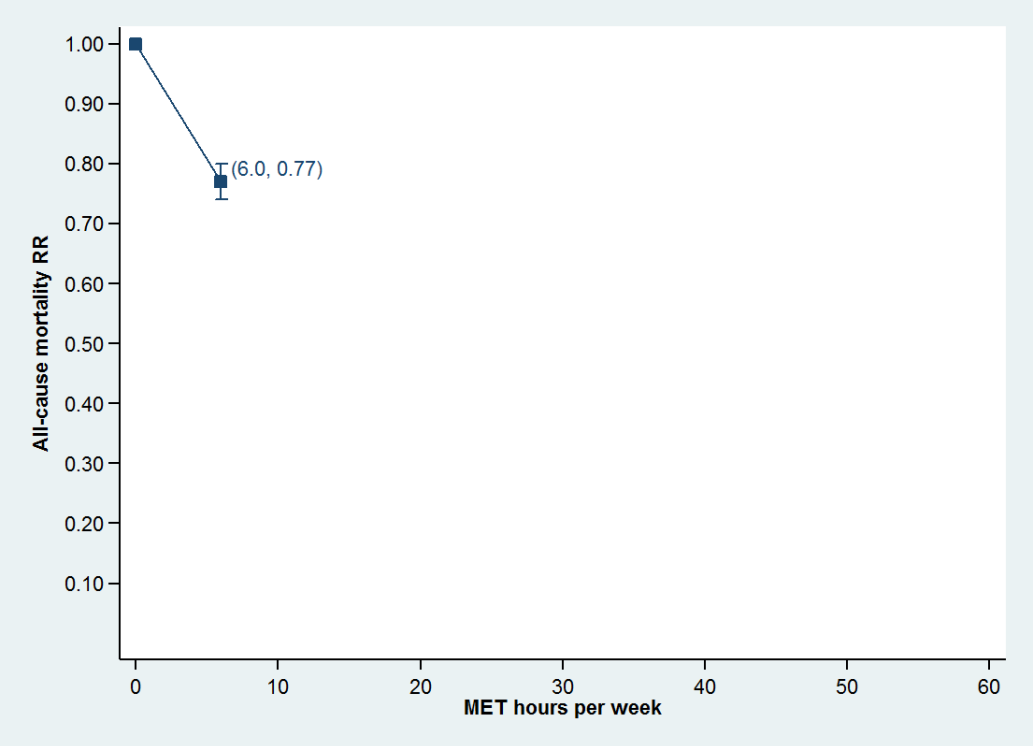
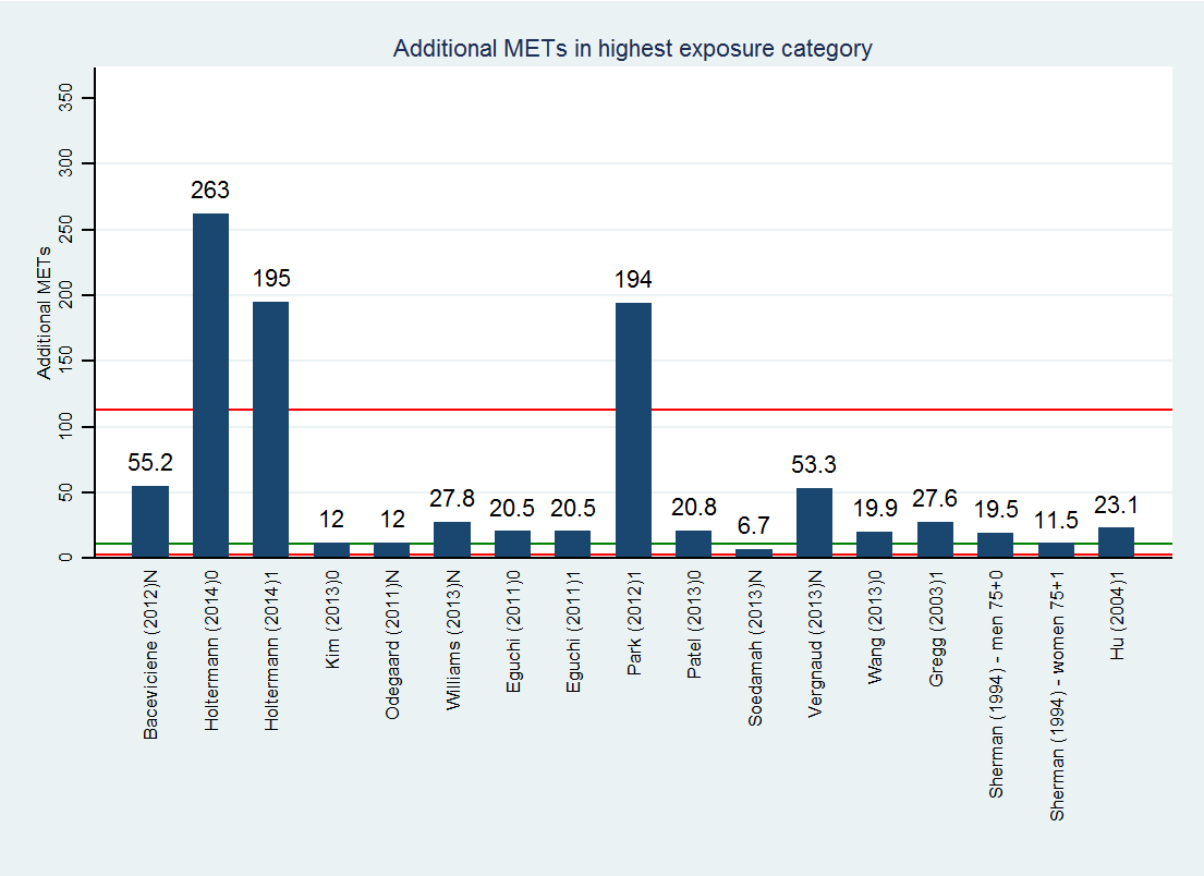


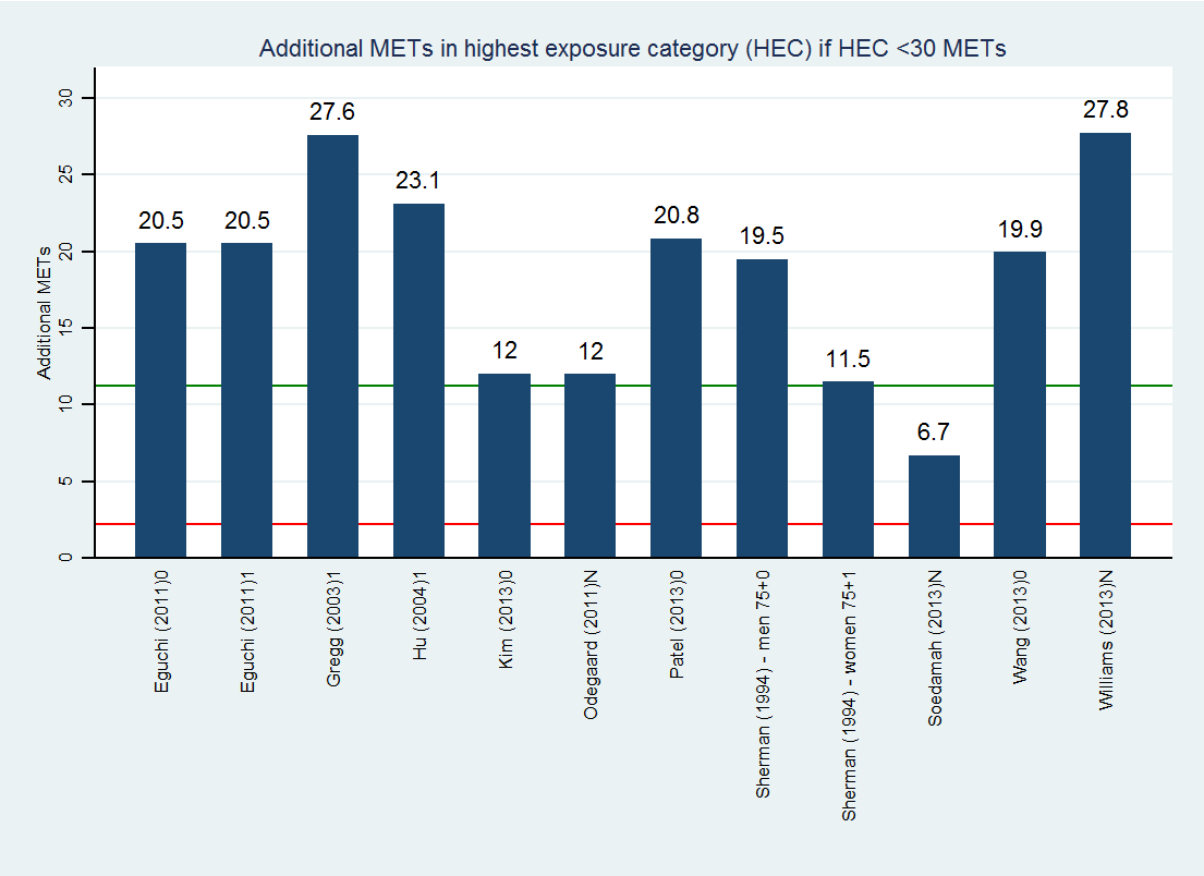
Figure S11. Chart showing additional MET hours per week in highest exposure category for CVD mortality studies



The green line indicates the recommended PA level of 11.25METhr/week

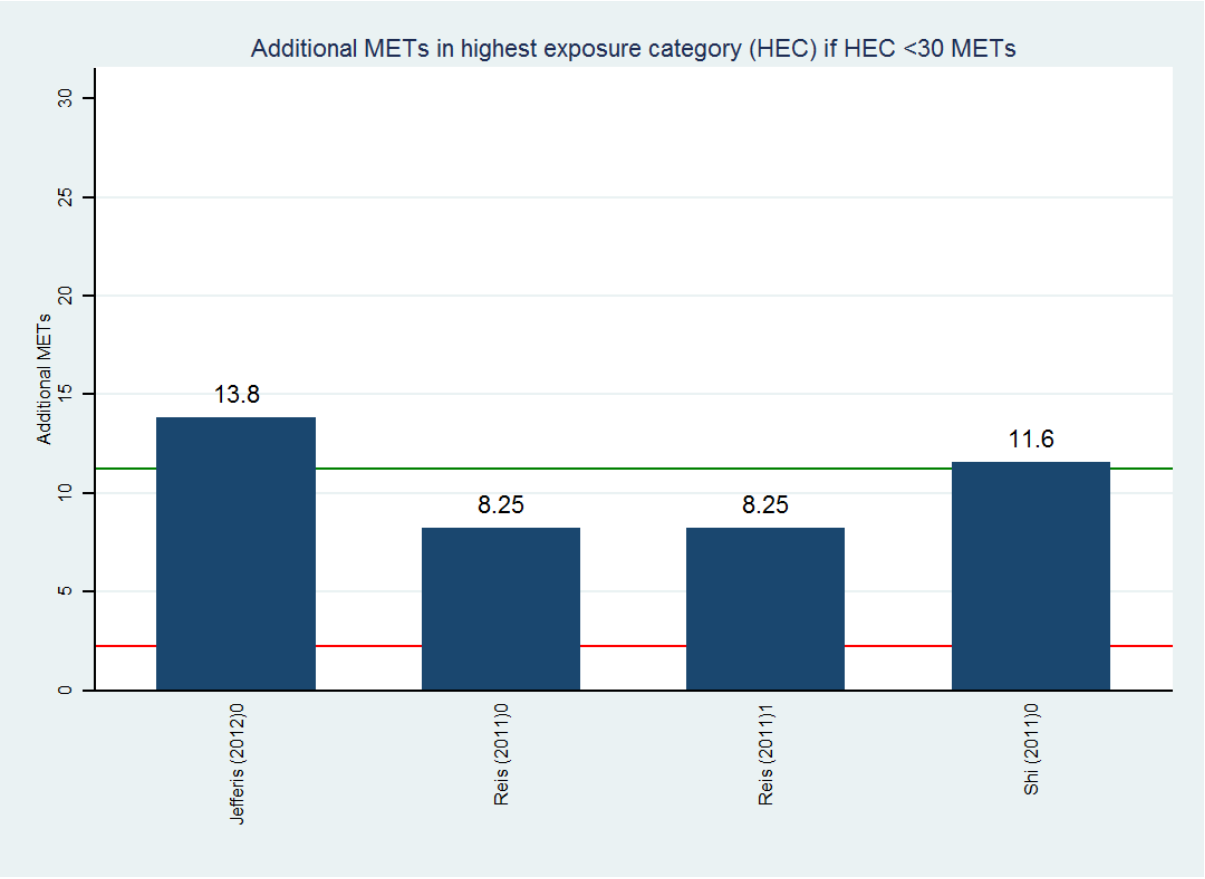
The red lines indicate the threshold for implausibly high levels (10 times the recommendation) or implausibly low (less than 30 minutes as demonstrated by the lower line)

Figure S12. Chart showing additional METs of less than 30 in highest exposure category CVD mortality studies



Please note the green line relates to recommended PA of 11.25METs, compared with the red line this time pertaining to the lower limit of <30 mins per week.

Figure S13. Chart showing additional METs of less than 30 in highest exposure category for T2DM incidence studies

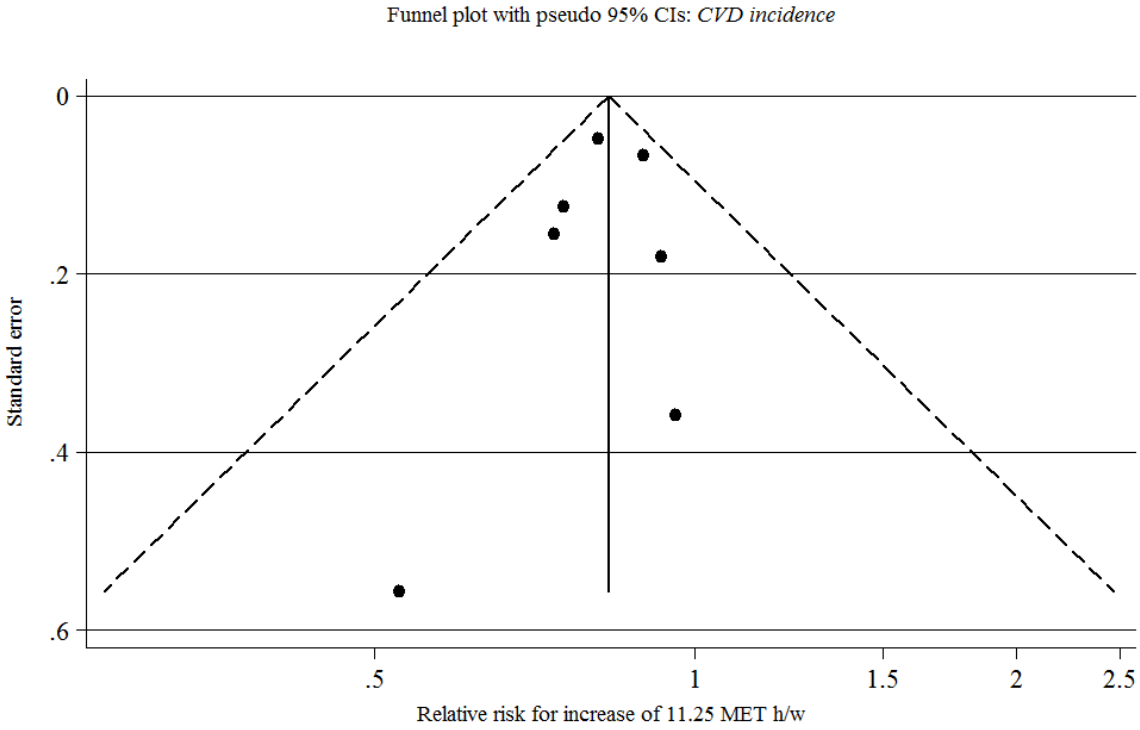


Please note the green line relates to recommended PA of 11.25METs, compared with the red line this time pertaining to the lower limit of <30 mins per week.

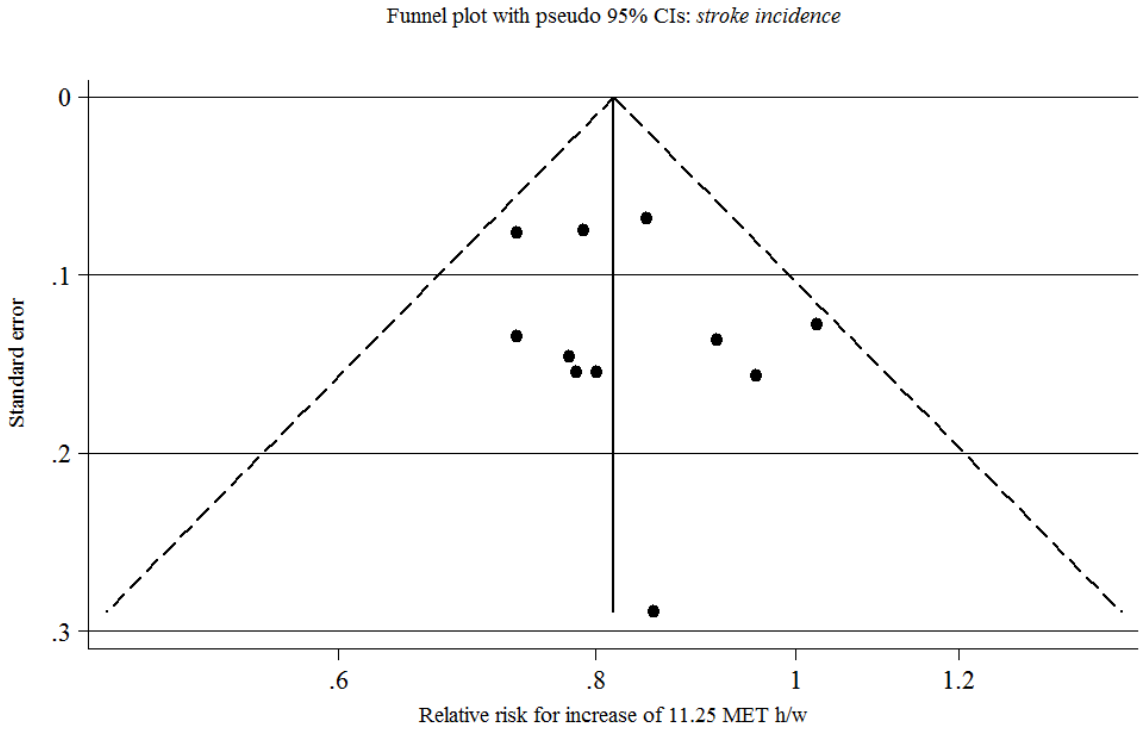
Figures S14—S20: Funnel plots for meta-analyses of 11.25 METhr/week increase in physical activity for cardiovascular disease and diabetes health outcomes

Meta-analysis results are displayed for all the power 0.25 analyses, adjusted for body weight. Conditions are given in the figures.

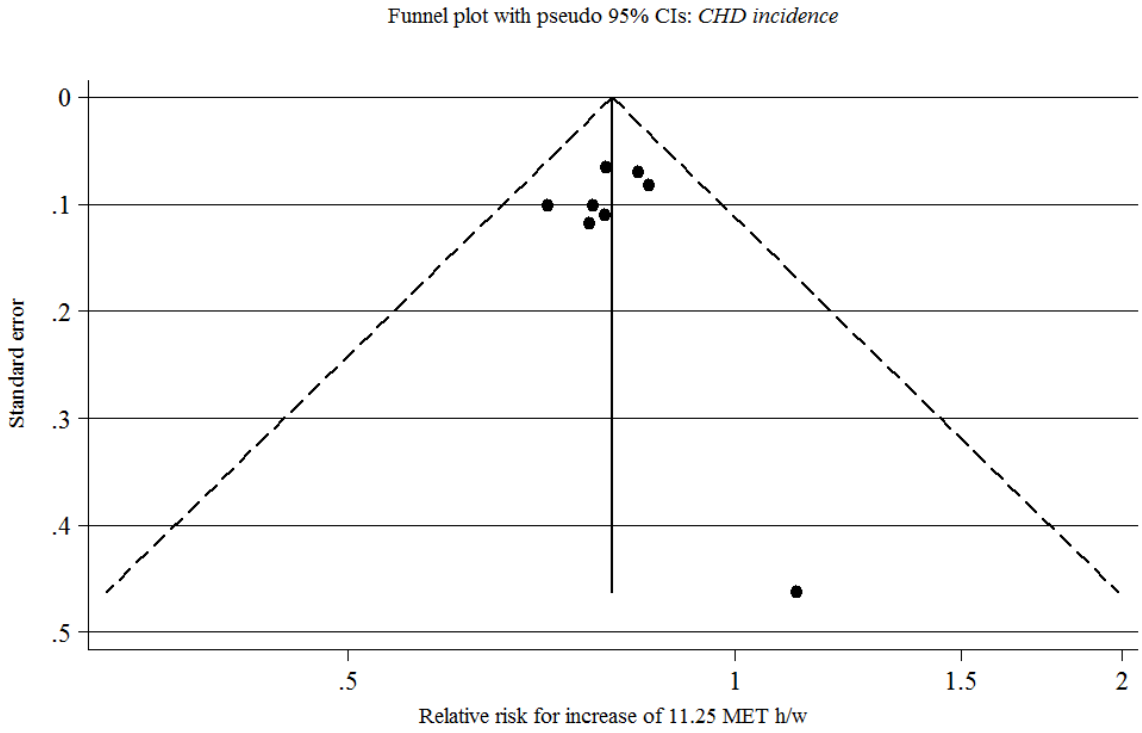
S14: CVD incidence



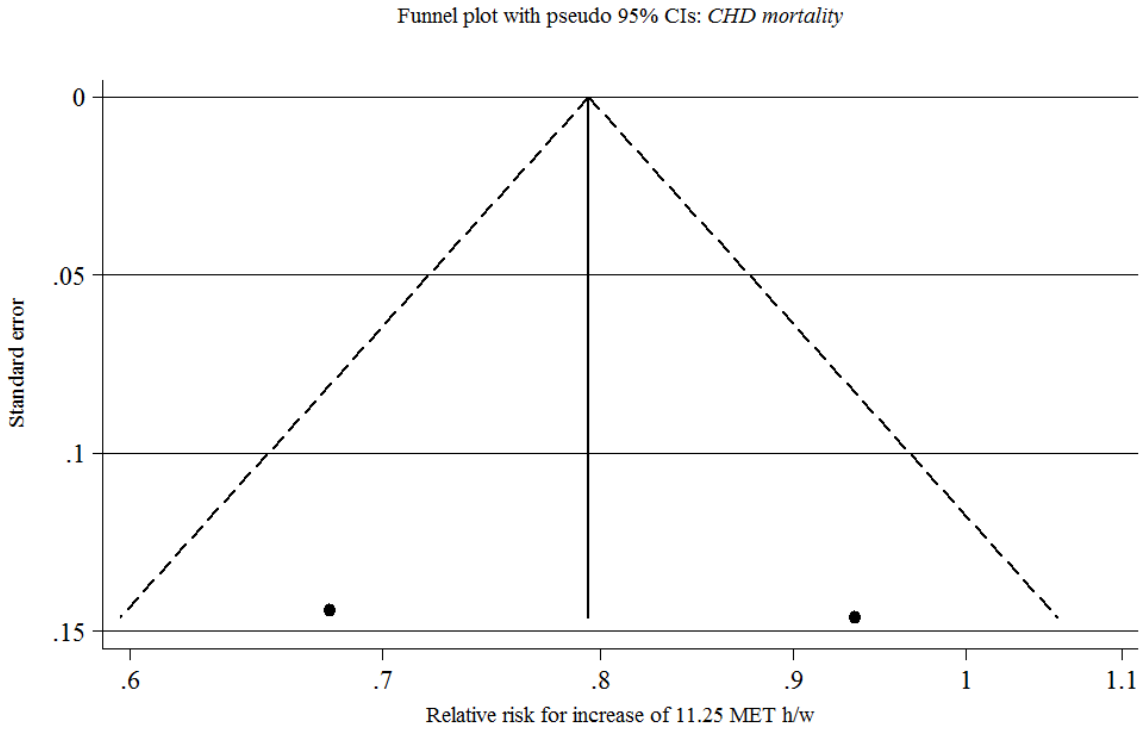
S15: Stroke incidence



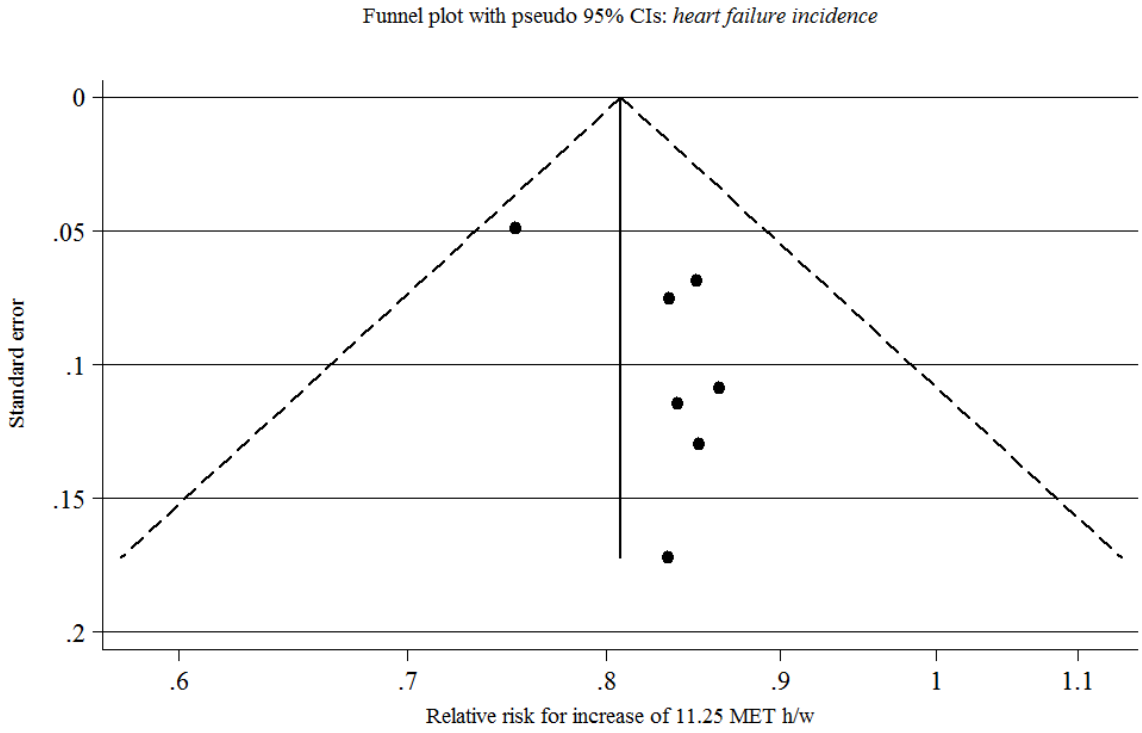
S16: CHD incidence



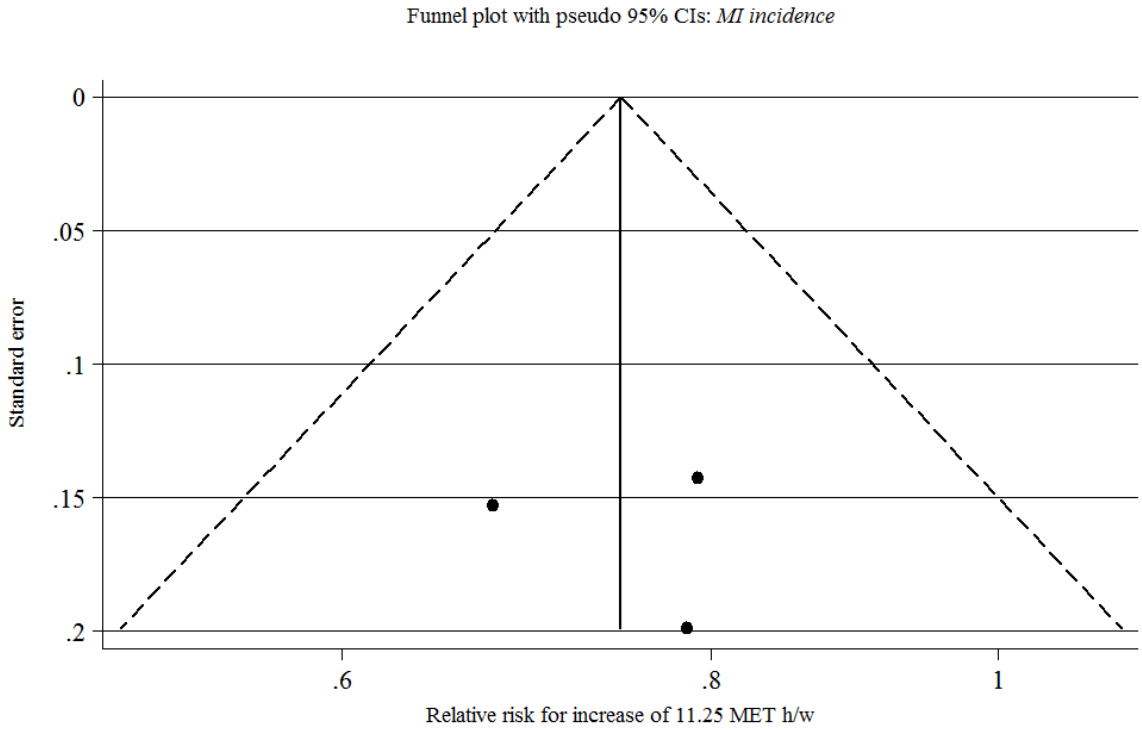
S17: CHD mortality



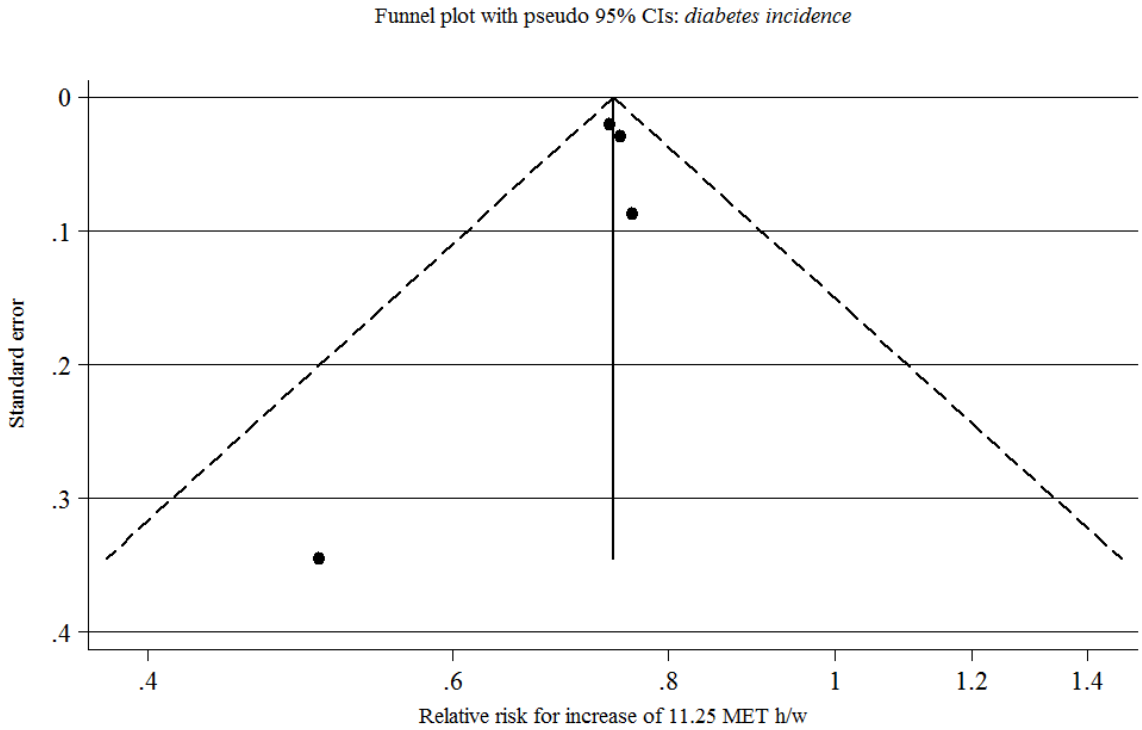
S18: Heart failure incidence



S19: MI incidence



S20: Diabetes incidence



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